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PUBLIC HEALTH SERVICE

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FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

SUBCOMMITTEE OF THE ANTIVIRAL DRUGS ADVISORY COMMITTEE

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OPEN SESSION

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WEDNESDAY, JANUARY 14, 1998

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The Open Session took place in Potomac Rooms I, II and III, Quality Suites, 3 Research Court, Shady Grove, Rockville, Maryland, at 8:00 a.m., Henry Masur, M.D., Chair, presiding.

PRESENT:

HENRY MASUR, M.D.	Chair
RHONDA W. STOVER, RPh	Executive Secretary
WAFAA EL-SADR, M.D.,MPH	Member
DARRELL ABERNETHY, M.D.,Ph.D.	Consultant (voting)
SUSAN COHEN, B.S.	Consultant (voting)
BARTLEY P. GRIFFITH, M.D.	Consultant (voting)
LAWRENCE G. HUNSICKER, M.D.	Consultant (voting)
STEVEN PIANTADOSI, M.D., Ph.D.	Consultant (voting)
STEVE SELF, Ph.D.	Consultant (voting)
E. STEVE WOODLE, M.D.	Consultant (voting)
ILEANA PINA, M.D.	Consultant (Non-voting)

PRESENT: (continued)

RANDALL C. STARLING, M.D.	Guest (Non-voting)
MICHAEL ELASHOFF, Ph.D.	FDA Representative
PAUL FLYER, Ph.D.	FDA Representative
MARK GOLDBERGER, M.D., MPH	FDA Representative
JOYCE KORVICK, M.D.	FDA Representative
RICHARD D. MAMELOK, M.D.	Sponsor Representative
LESLIE W. MILLER, M.D. FACC	Sponsor Representative
MARY J. STEMPIEN, MS, M.D.	Sponsor Representative

ALSO PRESENT:

DALE RENLUND, M.D.
JON KOBASHIGAWA, M.D.
GARY G. KOCH, Ph.D.
ANDREW NICHOLLS, M.D., Ph.D.

I N D E X

P R O C E E D I N G S

Time: 8:11 a.m.

CHAIRMAN MASUR: I think we're ready to call the meeting to order. I think we finally established a quorum of the committee. So we're pleased to call this subcommittee meeting of the Antiviral Drugs Advisory Committee to order.

As, hopefully, everybody here knows, we're here to discuss the drug CellCept from Syntex for immunosuppression following cardiac transplantation.

I'm Henry Masur from the Clinical Center, NIH. Before Rhonda Stover provides some information on conflict of interest, I'd like to introduce the panel members and the other individuals from the agency at the table. So if we could start from left to right, introducing the new Division Director, Dr. Goldberger.

DR. GOLDBERGER: Mark Goldberger, Director, Division of Special Pathogen, Immunologic Drug Products.

DR. KORVICK: Joyce Korvick, Medical Reviewer.

DR. ELASHOFF: Mike Elashoff, statistical reviewer.

DR. FLYER: Paul Flyer, statistical team

leader.

MS. COHEN: Susan Cohen, consumer member.

DR. HUNSICKER: Larry Hunsicker from the University of Iowa, a nephrologist who is involved with transplantation.

DR. WOODLE: Steve Woodle from the University of Chicago, transplant surgeon.

MS. STOVER: Rhonda Stover, FDA.

DR. SELF: Steve Self, Cancer Center, University of Washington.

DR. PIANTADOSI: Steve Piantadosi, Johns Hopkins. I'm a clinical trialist.

DR. GRIFFITH: Bart Griffith, cardiac surgeon, University of Pittsburgh.

DR. STARLING: Randy Starling, transplant cardiologist, Cleveland Clinic.

DR. PINA: Ileana Pina, Director of Heart Failure, Temple University.

CHAIRMAN MASUR: Thank you. Rhonda Stover, the Executive Secretary of this committee, now will read the conflict of interest statements.

MS. STOVER: The following announcement addresses the issue of conflict of interest with regard to this meeting, and is made a part of the record to preclude even the appearance of such at this

meeting.

Based on the submitted agenda and information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting, with the following exceptions.

In accordance with 18 U.S.C. 208(d), full waivers have been granted to Dr. Henry Masur, Dr. Wafaa El-Sadr, and Dr. Steven Piantadosi.

In addition, a limited waiver has been granted to Dr. Ileana Pina. Under the terms of the limited waiver, Dr. Pina will be permitted to participate in the subcommittee's discussions of CellCept, but she will be excluded from participating in any vote relating to the product.

A copy of these waiver statements may be obtained by submitting a written request to FDA's Freedom of Information Officer located in Room 12A30 of the Parklawn Building.

In the event that discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude

themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask, in the interest of fairness, that they address any current or previous involvement with any firm whose products they may wish to comment upon.

CHAIRMAN MASUR: Thank you.

Wafaa, perhaps you could introduce yourself. We've gone around the table and introduced the other committee members.

DR. EL-SADR: Wafaa El-Sadr, Harlem Hospital, Columbia University.

CHAIRMAN MASUR: With the audio system, I suspect it's hard to understand. Can we somehow get rid of this echo? All right.

All right. We appreciate the packet of information that's been supplied as background by the agency and the sponsor. We'll begin with the FDA introduction from Mark Goldberger.

DR. GOLDBERGER: Okay. I'd like to again extend our welcome to both the committee members and the company. We'd like to particularly thank Roche for bringing this application forward so that we have the opportunity to discuss it in a public setting like this.

I think that everyone involved in the field recognizes what a considerable undertaking it was to perform a study of this magnitude in cardiac transplantation. I think many people, both involved and not involved, with this would consider this among the finest, if not the finest, study actually ever done in this particular area.

Nonetheless, as happens in many studies, there were a few unexpected developments during the conduct of the study and in the results. We will be seeing some comment about that from both the company during its presentation and the FDA during our presentation.

We are particularly fortunate to have on the committee, as convened this morning, a lot of expertise, both in the biostatistical portions and in the clinical assessment of some of the issues that this study raises; and I think it wills be very instructive to hear comments from both of those perspectives during the course of the discussion.

Once again, let me just extend my thanks. Because we're on a relatively tight time schedule to accommodate some of the speakers, I think we'll probably just go right ahead now, if that's okay.

CHAIRMAN MASUR: All right. We'll move

ahead with Mary Jean Stempien, the Director of Medical Research for Roche, who, I presume, will introduce the program.

DR. STEMPIEN: Good morning. Distinguished committee members, it is my pleasure today to introduce Roche's presentation regarding the use of mycophenolate mofetil in cardiac transplantation.

My name is Mary Jean Stempien. I'm Director of Medical Research at Roche and one of the physician members of the mycophenolate development team.

Following my introduction, Dr. Richard Mamelok, also from Roche, will present the primary efficacy study of our submission, both its design and the results. He will be followed by Dr. Leslie Miller, who is Professor of Medicine and Director of the Cardiovascular Division at the University of Minnesota, who will offer his clinical interpretation of the study results.

In addition, we have brought with us three additional experts who, while not making a formal presentation this morning, are available to participate in any discussion or respond to questions, as appropriate.

They include Dr. Jon Kobashigawa, who is Medical Director of Heart Transplant Services at UCLA. He was the Chair of the Protocol Steering Committee.

Also, Dr. Dale Renlund is with us. He's Medical Director of the Cardiac Transplant Program at University of Utah. Dr. Renlund was one of our principal investigators on the trial.

Lastly, we have Dr. Gary Koch, who is Professor of Biostatistics at the University of North Carolina.

We are here today, because Roche is seeking recommendation from this committee regarding approval for use of mycophenolate mofetil, an immunosuppressant in cardiac transplantation.

CellCept, or mycophenolate mofetil, is currently approved for the prophylaxis of organ rejection in patients receiving allogeneic renal transplant. This committee reviewed that original NDA about two and a half years ago, during 1995. CellCept is to be used in combination with cyclosporine and corticosteroids.

The basis of this renal indication was three primary efficacy studies. They were all randomized, double blind, controlled trials. All three of these studies demonstrated that mycophenolate

reduced the incidence of biopsy proven rejection or treatment failure during the first six months post transplant, compared to control therapy.

We now propose an extension to this indication, such that CellCept would be indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal or cardiac transplants. Again, CellCept would be used in combination with cyclosporine and corticosteroids.

The primary efficacy study of this submission is our cardiac study 1864. As Dr. Goldberger has already mentioned, this was the first double blind, randomized, controlled trial of an immunosuppressant conducted in cardiac transplantation. As such, there was no precedent in a rapidly evolving field of medicine at the time of the trial design.

Because of this, we had special challenges, both in terms of the design of the study and also later additional challenges in terms of data interpretation, which will be elaborated on by Dr. Mamelok and Dr. Miller.

This slide shows members of our steering committee for the protocol. The steering committee was made up of a subset of the principal

investigators. We have three members of the steering committee with us, as I mentioned, Dr. Kobashigawa who was the Chair, Dr. Miller who will be making part of this presentation, and Dr. Renlund.

The outline of our presentation is as follows. Dr. Mamelok will provide some information on the earlier demonstrated efficacy of mycophenolate in our renal studies which we are using as a foundation for our extension into cardiac.

He will discuss the primary study 1864, the design challenges, the results, safety and conclusions, and then Dr. Miller will give his clinical perspective. Then I will return for a few closing remarks.

Dr. Miller is under a time constraint this morning. He will have to leave by about 10:30 to go to the ISHL team meeting. So we will try to have him available to answer questions first, if that's possible, when we come to that.

So at this point I'll turn the podium over to Dr. Richard Mamelok, who will tell you about our primary study.

DR. MAMELOK: Thank you, Mary Jean. Good morning. Just one minor clarification, for those of you who either think you're about to miss an ISHL team

meeting or maybe going to Puerto Rico and finding you're going to the wrong meeting. It's actually the ASTP meeting that Dr. Miller is going to.

That aside, the presentation is outlined here as presented by Dr. Stempien. First I'm going to touch on the renal program, because it forms the foundation for the transplant work done with mycophenolate in cardiac transplantation.

The renal program consisted of three double blind, randomized, clinical trials, two of which were controlled with azathioprine, one with placebo. One trial was carried out in the United States. One trial, the one in the middle, so called tri-continental trials, and then the third trial, the placebo controlled trial, was carried out in Europe.

The doses of mycophenolate tested were 1gm BID and 1.5gm BID concomitantly with cyclosporine and corticosteroids. 990 patients received mycophenolate in those trials.

The results show that in all three trials mycophenolate produced a clinically and statistically significant reduction in biopsy proven rejection and treatment failure, treatment failure being defined as those patients who either died or withdrew from the trial prior to experience a biopsy proven rejection

event.

The orange bars are the azathioprine controls. The blue bars are the two doses of mycophenolate. The pale bar here is the placebo control, and again the two blue bars are the two doses of mycophenolate, all showing a difference.

I'm now going to spend the rest of my time discussing study 1864, which is the controlled trial in cardiac transplantation.

When the cardiac program was planned, it was discussed with FDA that, if the three renal trials that were then currently underway demonstrated efficacy and safety, then one well controlled, randomized, blinded trial in cardiac transplantation would be enough to extend and support an extension of the indication, if the totality of the data in the renal and the cardiac program so warranted.

1864 is that well controlled trial, and what we're here today to do is to discuss the totality of that data.

The objective of the trial was to compare the safety and efficacy of mycophenolate with azathioprine, each in combination with cyclosporine and corticosteroids in cardiac transplantation.

We met two challenges in this trial. One

was the choice of the control, and the other was the choice of primary endpoint.

The first challenge of control: In a recent compilation of the database, 83 percent of cardiac transplant patients are currently treated with a combination of so called triple therapy consisting of cyclosporine, azathioprine, and corticosteroid.

This corroborates what investigators told us when we planned the trial, that triple therapy was the standard of care and, therefore, we could not do a placebo controlled trial but were required to do a controlled trial with azathioprine, because the investigators felt that it would be unethical to withdraw the standard of care from their patients.

The doses chosen of azathioprine were those recommended by the investigators and were chosen to suit what they felt were adequate doses in their -- by their experience and ones used at their centers.

The development of modern therapy for cardiac transplantation has followed a lengthy course. In the late 1960s the combination of steroids and azathioprine, which I will refer to as double therapy, really initiated the advent of successful cardiac transplantation, with one-year survival rates of about 50 percent.

In the early 1980s cyclosporine was introduced, and at that time various empirical regimens were tried, often dropping azathioprine and using double therapy or therapy with cyclosporine and corticosteroids, but over the course of the eighties and by the late eighties or early 1990s, triple therapy of cyclosporine, steroids and azathioprine has become the standard of care, based on more or less a trial and error approach.

The presence of activity of azathioprine in cardiac transplantation, especially in the context of triple therapy, is based on historically controlled studies and on large databases. We conducted a literature search spanning the time from 1980 through 1997.

The extent of this search was wide in that we wanted to capture as many papers as possible touching on the use of azathioprine in cardiac transplantation, but we then focused on those papers that describe the combination of double therapy versus triple therapy within the paper itself.

These are studies that we identified that directly compared cyclosporine and steroids to triple therapy. The publication is listed here. The number of patients in each of these descriptions is listed in

the two columns for triple and double therapy.

This column lists the delta of survival that is the difference of survival by subtracting the one-year survival rate on double therapy from the one-year survival rate on triple therapy. So a positive number means that triple therapy gave a better survival.

As you can see, the range of one-year survivals in these experiences is wide, ranging from four percent to 22 percent, and just to benchmark this a little bit, in Dr. Opelz' database the triple therapy gave a one-year survival of 82 percent, and double therapy gave a one-year survival of 78 percent.

In Dr. Copeland's study the triple therapy gave a one-year survival of 94 percent for triple therapy, and a one-year survival of 72 percent for double therapy. In the other experiences the survival rates are in those ranges.

The five-year survival rate in Dr. Opelz' study: The difference was nine percent, and that was statistically significant at p .001. The five-year survival in Dr. Copeland's study was -- the difference was 29 percent in favor of triple therapy.

One other item to note is that in Dr. Bolman's study he also reported the number of episodes

per patient of rejection, and there were .84 episodes of rejection in the double therapy and .29 episodes per patient of rejection in the triple therapy.

Because all of these studies and databases are confounded by time, because they come from different centers, probably reflecting somewhat different practices, and they are from possibly somewhat different populations, formal cross-study comparisons are difficult and not appropriate, but in all of them azathioprine consistently is associated with improved results compared to double therapy.

I'm now going to turn my attention to the choice of primary endpoint. This is made difficult when looking at rejection in cardiac transplantation, because both the detection and quantification of rejection in cardiac transplantation is imperfect and evolving, and Dr. Miller will address this later in his part of the talk.

When we designed this trial, as has been mentioned before, there was really no well controlled trial and no precedent for designing such a trial. No one had to choose a primary endpoint before in cardiac transplantation and focus only on one.

So there was no information, really, on either specificity or sensitivity of any rejection

endpoint. This is partly reflected in the trial as well, as two amendments were undertaken during the blinded portion of the trial changing the primary endpoint, in part mirroring changing opinion within the cardiac transplant community.

We settled on two co-primary endpoints in discussions with FDA. One was death or retransplantation, and the hypothesis was that mycophenolate would be equivalent to azathioprine for death and retransplantation at one year.

The second endpoint was that was biopsy proven rejection with hemodynamic compromise, and the hypothesis was that mycophenolate would be superior to azathioprine at six months post transplant, and the intent was to meet both of these endpoints.

The protocol had a variety of specified secondary rejection endpoints. They can be divided into two general categories, those that required proof by biopsy of rejection and those that didn't. Those that required biopsy proof were by ISHLT grade.

Grade 3 here is grade out a little bit. That is not a protocol specified endpoint, but was asked for -- an analysis asked for by the steering committee prior to unblinding the trial.

Post-treated biopsy proven rejection,

incidentally, was the first primary endpoint when the trial actually started in 1994.

The endpoints that do not require biopsy proof were patients who required post-treatment for rejection, whether or not they was biopsy proof, and patients who required OKT3 or ATG as therapy for rejection.

1864 is a double blind, randomized, multi-center trial. The AZA control doses ranged from 1.5 to 3 milligrams per kilogram per day, and as I mentioned, were chosen by the investigators to reflect their standard of care. The dose of mycophenolate was 1.5 grams BID or a total of 3 grams a day. Both were given with concomitant immunosuppression consisting of cyclosporine and corticosteroids.

The study plan here is outlined. Patients were randomized prior to transplantation, before they were transplanted, and then were to receive study drug within five days of their transplantation.

The endpoint for rejection is measured in all patients, whether still on the trial or withdrawn, at six months, and the mortality endpoint is measured at one year in all patients, whether still on active study drug or withdrawn from the trial.

Adverse events are collected while

patients are on study drug. The trial continues for three years for the purpose of collecting long term safety data, and the safety data we're collecting on all patients, whether still on study drug or not, includes the development of malignancy and mortality.

We are also collecting coronary vascular disease data by angiography on all patients that are able to have an angiogram at three years.

We have provided as part of the NDA update, the safety update required, safety data on nine months' additional experience to what was provided in the original NDA.

Data was collected on all randomized patients, both on study and post-termination, for both primary endpoints.

Patient disposition within the trial is shown on this flow diagram. Eleven percent of patients dropped out of the trial without getting one single dose of study drug, and this was unanticipated.

There were 650 patients enrolled in the trial, equally distributed to azathioprine and mycophenolate. Seventy-two patients dropped out before receiving study drug. They were blinded. So they dropped out. No one knew what drug they were assigned to, and that left 578 patients in the treated

group.

Of the patients who dropped out, 74 percent received azathioprine as part of their immunosuppressant therapy post-transplant. So for those patients who were assigned to get mycophenolate they, in fact, got azathioprine, the control, instead.

To emphasize, this withdrawal of the patients was done without knowledge of what study drug the patient was assigned to, and as I'll talk about later, that leaves a treated group which we think is an appropriate group to analyze, both because it is biologically sensible to analyze patients who actually got the study drugs that one is studying, and the treatment assignments within this group remain randomized because of these patients withdrawing without any -- not as a factor of what they were assigned to.

I'm now going to move to the results in 1864, and first focusing on the 650 patients who were enrolled in the trial. The presentation will be divided into first talking about death and retransplantation, and then talking about rejection.

For death and retransplantation, this includes on study and post-termination events for all patients, and the CMH type weighted difference

adjusted by investigator was the method used to analyze the data.

In the enrolled population the death and transplantation rate at one year was 2.6 percent lower in the mycophenolate assigned patients, which was in the range for statistical equivalence.

For practical purposes, this endpoint measures death. There were four patients who were retransplanted -- met this endpoint by retransplantation, and 87 patients met this endpoint by dying.

These data are shown in somewhat more detail on this table, with the treatment difference of 2.6 percent, and the lower limit of the confidence interval of -2.5 percent; and these data are depicted graphically on this slide.

The abscissa shows the percent difference in deaths, subtracting the mortality rate of mycophenolate from the mortality rate of azathioprine. So a negative number to the left of this line would indicate that azathioprine was giving lower mortality rates. A positive number over here would indicate that mycophenolate patients were surviving at a better rate.s

The area between these hatched areas, this

clear blue area here, is what was defined as the range of equivalence, and this range of equivalence was set primarily to calculate sample size. In discussions with the agency, it was acknowledged from the beginning that, in fact, some clinical judgments would also have to go into deciding whether a statistically equivalent event was also clinically acceptable in terms of making a judgment that equivalence actually existed.

This is a Kaplan-Meier curve showing the occurrence, the cumulative incidence of death or retransplantation in the first year. The blue curve is mycophenolate. The orange curve is azathioprine. These are not statistically different, but there are some qualitative things to note.

Early on, the mortality rate in mycophenolate was higher than in azathioprine, and this difference in mortality is accounted entirely for difference in mortality in the untreated group. It's notable that the lines cross at about seven months, and separate then in the opposite direction, and longer term follow up of these patients indicates that this trend that's seen at 12 months is continuing. This figure, I think, is Figure 9 in the background package that you were provided.

I'll now turn my attention to the rejection endpoint. Again, this includes on-study and post-termination events for the first six months. The endpoint was biopsy proven rejection with hemodynamic compromise tested by the CMH test.

This is the definition of hemodynamic compromise that was prospectively set out in the protocol. It was first defined in the protocol from the inception as a definition to guide pulse immunosuppressant therapy. That is, it was not originally intended to be an endpoint.

There was also a category of "Other," and this category allowed clinicians to account for patients who they felt had significant -- clinically significant important hemodynamic compromise that -- but that did not fit any of these categories. Any of these categories had to occur with a positive biopsy in order to meet the definition.

In the enrolled population there were no differences between the azathioprine and the mycophenolate group for this endpoint.

These again are the protocol specified secondary rejection endpoints. For those, there's a detailed table, Table 17, in your background package that gave the specific numbers, but the range were two

percent to six percent lower in the mycophenolate assigned patients, but none were statistically significantly different.

So in conclusion, from the enrolled population we conclude that mycophenolate is at least as good as azathioprine for the prevention of death and prevention of rejection in cardiac transplantation.

I'm now going to present data in essentially the same order and same format that you just saw. This time it will be for the treated population.

We think that the conclusions drawn from the enrolled population alone is limited because of this issue of 11 percent of patients never receiving any study drug whatsoever. Most untreated patients were treated with the control, and the differences in treatment effects will, therefore -- if they truly exist, will be diluted in the enrolled population. The treated population, therefore, is more pharmacologically relevant.

There were 578 patients in the treated population, equally divided between azathioprine and mycophenolate. To get into the treated population, one had to receive one dose of study drug. So one

dose or more of study drug got you into the treated population.

The treatment assignments are random in the treated population. The treatment assignments were blinded when the decision was made to withdraw patients from the trial. Events leading to withdrawal, therefore, are unrelated to treatment assignment, and thus treatment comparisons in the treated population are valid, because the treatment assignments remained random.

A variety of baseline variables were examined and were balanced for all of those listed here between the azathioprine and the mycophenolate groups in the treated population.

Efficacy again, measured by death or retransplantation, and for death and retransplantation the hypothesis again was MMF would be equivalent to azathioprine at one year, and the results are shown on this slide.

The mortality rate, the death and retransplantation rate -- I think it was one patient who was retransplanted. The rest are deaths -- was 11.4 percent in the AZA group, 6.2 percent in the mycophenolate group, with a difference of 5.3 percent, and the lower limit of the confidence interval of that

difference at 97.5 percent was .9 percent. The lower limit is +.9 percent.

These are again shown graphically with the range of equivalence depicted here. Here's the observed difference. The way equivalence was defined, it was a one-sided test, indicated here, and the lower limit of the confidence interval does fall within the range of statistical equivalence; but because it's greater than zero, one can say that there is, in fact, a statistically significant difference in survival between mycophenolate and azathioprine group.

We know that the issue of robustness is one to contend with in this situation, and that the FDA has examined this. We believe that, at least it is our understanding, the method they use is not one that we fully agree with, and we would be happy to comment on that later in the discussion period, if the committee so desires to get into that discussion.

The Kaplan-Meier curve in the treated group is depicted here. For the first three or four months, the curves overlap, and then at about four months they begin to separate and continue to separate up to 12 months, and again in the updated safety information this trend continues.

In conclusion, in the treated population

we met the protocol definition for statistical equivalence. In the treated population mycophenolate patients have a better survival than azathioprine patients, and there was support for concluding that mycophenolate may be better than azathioprine in preventing death or retransplantation.

For the rejection endpoint, biopsy proven rejection with hemodynamic compromise, again looking at all patients in the treated group receiving one dose or more for a full six months, whether or not they were in the trial; and the results are shown here.

There's a small percent difference, but this difference is not statistically significant, and these differences are very small.

When these data were shown to our steering committee at the level you saw it now without any patient level information, the steering committee noted that the rate of hemodynamic compromise that they saw was at least twice as high and possibly higher than what they thought it would be in the control group.

This led them to wonder about the endpoint and whether it was really, in hindsight, so to speak, the best endpoint. The steering committee then

suggested a more restrictive definition for hemodynamic compromise, which we denote as severe hemodynamic compromise cardiogenic, mostly to just differentiate it from the primary endpoint in the protocol.

This list here is the entire list that was used for the primary endpoint. The terms highlighted in yellow are those terms which met the definition for severe hemodynamic compromise. That is, an ejection fraction of less than 30 percent, fractional shortening of less than 20 percent, or the need for inotropic support. You could meet this endpoint if any one of these occurred in conjunction with a positive biopsy.

The steering committee designed this endpoint to detect the sickest patients who they felt would have clinically apparent and symptomatic congestive heart failure.

This definition of severe differs from a protocol specified definition of severe, which defined severe hemodynamic compromise as hemodynamic compromise that was designated by any of these factors from fractional shortening on above -- so any of these -- in combination with inotropic support.

So the difference is that the one the

steering committee recommended also had inotropic support existing by itself. The one in the protocol, which was originally, again, defined as a guide to immunosuppressant therapy, said that inotropic support had to be combined with these.

The reason we think that the committee's definition is better than the protocol one that was designed for treatment is that the protocol one will miss patients who receive inotropic support alone in conjunction with a positive biopsy without having happened to have any of these other things reported.

It was felt by the committee that that group of patients represents a sick group of patients, and in the presence of rejection likely to be due to rejection.

The results of this analysis is shown in this panel and provided to compare to the original definition of hemodynamic compromise here, azathioprine in orange, mycophenolate in blue. There was a 17 percent incidence of biopsy proven rejection with severe hemodynamic compromise in the azathioprine group, and an 11 percent incidence in the mycophenolate group.

We looked at the one year survival when combining the treatment groups. So the full 578

patients, defining them by those who met the definition of severe hemodynamic compromise, and compared those who did not meet the definition of biopsy proven rejection with severe hemodynamic compromise.

In those patients meeting the definition overall, the mortality was 21 percent, and in the remainder of the patients it was seven percent.

This is a flow diagram showing how patients divided among the various categories, 578 patients. Fifty-seven developed biopsy proven rejection with severe hemodynamic compromise.

In this 57, there were 12 deaths. All 12 deaths occurred in the azathioprine group, and we find this very intriguing and of great interest, and Dr. Miller will comment on his clinical interpretation and the clinical meaning of that finding.

I'll now turn my attention to the secondary rejection endpoints. In the graphs and tables you will see, you will see nominal p values which should be interpreted with caution, but we believe there are appropriate ways to analyze them, but at a first cut we're presenting them as their nominal levels, and then asking you to look at the rejection data in its totality.

Here we see rejection divided by the most serious grade reached. Again, mycophenolate in orange, AZA in -- I'm sorry, mycophenolate in blue, AZA in orange.

For grade 1A rejection, the mildest form of rejection, essentially all patients get it sometime in the first six months, and there are no differences.

When we applied progressively tougher criteria to judge rejection so that patients who had to have at least a grade 2 biopsy, the rates diminished, and the difference is somewhat larger than here. When you apply -- looking at patients who were required to have at least a grade 3 level of rejection, again the overall rates diminished. The difference is eight percent between mycophenolate and azathioprine.

Another way to look at rejection is rejection requiring pulse immunosuppressive therapy in the course of -- in the post transplant course of these patients, and these data are shown here.

These are patients who were treated for rejection, whether or not they had biopsy proof of rejection. Seventy-four percent of patients in the AZA group needed treatment for rejection; 66 percent required it in the mycophenolate group.

For those who had biopsy proven rejection requiring treatment, -- again I'll just mention that that was the initial endpoint, primary endpoint, at the inception of the trial -- there's a difference of 71 percent versus 64 percent in favor of mycophenolate, and when one looks at the patients manifesting the most severe forms of rejection requiring OKT3 or ATG, the difference is 21 percent versus 15 percent, again in favor of mycophenolate.

So in conclusion, there was no difference between mycophenolate and azathioprine for the co-primary rejection endpoint. Mycophenolate appears more effective than azathioprine in preventing manifestations of severe rejection, as measured by ISHLT grade, as measured by the need for pulse immunosuppressive therapy, and by the occurrence of severe hemodynamic compromise ("cardiogenic"), again just to try and differentiate it from the other definition.

I'm now going to present some of the safety information relative to azathioprine. The safety profile of mycophenolate at 3 grams a day in cardiac transplantation is similar to the safety profile seen at both 2 and 3 grams a day in renal transplantation.

This slide shows the patients who had to prematurely terminate due to adverse events in study 1864 and in the azathioprine control trials in the renal program at comparable time points in each of those programs; that is, through the time when the last patient enrolled in the trial reached one year post transplant.

Within study 1864 the need to withdraw because of an adverse event was similar between azathioprine and mycophenolate, and when one looks across the experiences, the rates also appear to be similar. This gives a general indication of how adverse events in some general way were viewed in the context of the respective clinical setting in which they are observed.

The rest of the safety data I will present will be from study 1864 in cardiac transplant. These are t he adverse events that led to withdrawal or discontinuation or a reduction in dose or interruption in dose or discontinuation from study drug during the trial. As you can see, by far and away, the most common cause of that was leukopenia, and other events occurred with about the same frequency in the azathioprine and mycophenolate group.

The overall malignancy rate was 6.9

percent in both groups, both mycophenolate and azathioprine group, and these data are broken out by general categories of malignancy, lymphoma with a slightly lower rate in mycophenolate, non-melanoma skin with a slightly higher rate, mycophenolate, and a whole potpourri of other malignancies gave about equal rates.

These data indicate that the overall rates of malignancies were the same in both groups.

There were more opportunistic infections occurring in the mycophenolate patients compared to the azathioprine patients, and the most common opportunistic infections are shown on this slide. The major differences occurred in patients getting Herpes simplex, Herpes zoster, and CMV viremia.

Certainly, these infections are important infections in the transplant setting and one we all worry about. In some ways, we're fortunate, because there is treatment for these. So many patients can be adequately treated.

I failed to mention earlier, but would like to now, that the difference in mortality that we saw in the mycophenolate group was due to two things. It was due to a decrease of death due to rejection, and it was due to a decrease in death due to

infection.

The infections that the patients died from that made that difference were, in general, not virus infections, but they were bacterial and fungal infections.

So this excess of opportunistic infections did not seem to translate to increased mortality in the mycophenolate group.

This is a slide showing absolute neutrophil counts at various times in a patient's experience post transplant. In each major cell here, focus on the top line which are the patients who maintained neutrophil counts above 2,000, and the bottom line are patients who dropped below 500.

Most patients in both azathioprine and mycophenolate are able to maintain levels that are quite acceptable. There were a few patients here -- I think this is six patients here, two patients here in the mycophenolate group -- who did have neutrophil counts observed below 500, but again this low neutrophil count did not seem to translate into excess mortality in the mycophenolate group, quite the contrary.

So in conclusion, the safety profile of mycophenolate in cardiac transplant is similar to that

of mycophenolate in renal transplant, except that Herpes simplex and Herpes zoster infections are more common in mycophenolate patients compared to azathioprine in cardiac transplant, but these are, as I indicated, mostly treatable infections, albeit still associated with important morbidity.

The conclusions from 1864 are that mycophenolate is efficacious in preventing rejection in cardiac transplantation; that mycophenolate is effective in preventing mortality in cardiac transplantation. There is a favorable risk/benefit balance in favor of mycophenolate, and there is evidence to suggest that mycophenolate may be superior to azathioprine for cardiac transplantation.

We now move to Dr. Leslie Miller's talk, and he will give you his clinical perspective of the trial.

CHAIRMAN MASUR: Before Dr. Miller talks, are there any questions from the committee for the previous presentation? Questions for Dr. Mamelok? Bartley?

DR. GRIFFITH: Yes. You mentioned that to be enrolled and treated, you needed to take at least one dose. How many patients didn't complete their dosing as routine, once they received a dose?

DR. MAMELOK: Well, it depends a little bit on what time period you look at, but in the one year time frame in the mycophenolate group about 75 percent of patients dosed for a year. It was somewhat less than that -- I think it was 68 percent for the azathioprine patients.

If I could just ask one favor of the committee, if it would be all right with the Chair, because of Dr. Miller's time constraints, if we could limit questions to this part to just questions specifically related to a slide that I showed that were unclear, that you need clarified. Then any other questions in depth or controversial points or whatever, I'll be happy to discuss, but I'd prefer to do that later so that Dr. Miller has a full chance to give his talk and then answer questions before he has to leave.

CHAIRMAN MASUR: He has until eleven o'clock or 10:30?

DR. MAMELOK: Eleven.

CHAIRMAN MASUR: Eleven? Okay.

DR. MAMELOK: Would that be okay? I don't mind doing that. I just think the flow might be better if we do it that way.

CHAIRMAN MASUR: Okay, are there any other

pressing questions? Okay.

DR. MILLER: Thank you, Dr. Mamelok. Members of the panel, ladies and gentlemen, it's really a pleasure to have the opportunity to offer some comments on what I believe are some of the most pertinent clinical aspects of the large body of data that you just heard presented, and I'll do this from the perspective of both the clinician and the scientist.

I'd like to describe initially the status of heart transplantation today with regard to immunosuppression, and describe what I think is an unmet need.

Despite many advances in the field over the last 15 years, there has been essentially no change in the one-year survival since the introduction of cyclosporine in the early 1980s. Rejection remains the number one cause of death in the field of heart transplantation. If you also include infection related deaths, it's an overwhelming cause of first year mortality.

Despite our current approach to immunosuppression, at least half of the patients will exhibit one episode of acute cellular rejection and, unlike renal transplantation and other areas, there is

no dialysis equivalent following heart transplantation. So the patients who succumb and have graft loss, basically, die of this problem, and it is an increasing risk and why immunosuppression is a critical aspect of the therapy.

Secondly, over 40,000 patients have thus far undergone heart transplantation worldwide, and only two percent or approximately 700 patients have been offered retransplantation. So again, the stakes are high, and we need to be very effective in our immunosuppression and, unfortunately, to date have not been able to demonstrate a new advance.

This timeline basically describes the evolution in immunosuppression, and I show you this to point out the status of immunosuppression in heart transplantation. It's a rather sobering and humbling description in that, until the mycophenolate study, everything that we did in heart transplantation was based on single center experience with no controlled prospective randomized trial data.

Azathioprine and prednisone were introduced based on animal and renal transplant experience, based on two single-center experiences and nonrandomized data. We made a categorical change from azathioprine to cyclosporine based therapy, very

quickly realized that at the same dose of steroids, substituting that as the primary agent, we were unable to accept the toxicity associated with those doses of the drug.

At that point azathioprine was reintroduced into the regimen, and holistically adopted. If you remember the slide that Dr. Mamelok showed you, again in nonrandomized data, based on 31 patients, the observation that using three drugs would be an important advance. We categorically in the field switched to triple drug immunosuppressive therapy.

At a similar time point in the evolution of immunosuppression, there was an introduction of a very potent antilymphocytic antibody sera, referred to as OKT-3. This was to add immunosuppression in the early post-transplant period in the hopes of preventing rejection ever in the graft and developing or inducing tolerance. Hence, the term induction therapy.

Unfortunately, over the next eight years there were no prospective trials evaluating the impact and, although 50 percent of the centers around the country and around the world adopted OKT-3, there was absolutely no data to validate its superiority.

Finally, MMF trial, again conducted with azathioprine as a comparative control and, more recently, the cyclosporine tacrolimus trial, again using azathioprine as the control.

One observation is that, although OKT-3 was used clinically in a vast number of centers around the country without an approved indication for eight years, that has not become the standard in this health care economy where physicians try to prescribe a drug like mycophenolate which does not currently have a specific indication in hearts are often prevented from using that drug.

This is in bar graph trying to describe what I've just presented to you in text form, and that is that there has ben a continued improvement using azathioprine based immunosuppression until approximately 1980, but in the past 15 years we've seen essentially no change in one-year survival.

Finally, some comments about azathioprine in particular. I think that, as Dr. Mamelok has pointed out, we described using it as a primary agent in heart transplantation. We saw it was associated with approximately a 60 percent one-year survival.

When it was replaced with cyclosporine, it was at nearly the same doses of corticosteroids, but

I think, importantly, what the introduction of triple therapy, the reintroduction of azathioprine to the cyclosporine/prednisone regiment allowed almost a 50 percent reduction in the doses of both cyclosporine and prednisone without an associated decrease in survival and a significant reduction in side effects.

Similarly, the confidence in this regimen of cyclosporine/azathioprine led a number of investigators to utilize steroid-free immunosuppression and found that, in fact, they could use two-drug therapy with azathioprine and cyclosporine and be successful long term in up to 80 percent of patients.

So I think it's very clear that triple drug immunosuppression is the standard of practice in heart transplantation around the world.

Some other, I think, important comments for the panel with regard to some of the uniqueness of heart transplantation, particularly in contrast to renal transplantation where there is a clear, easily obtained biochemical marker. It can be followed very frequently to make the diagnosis or the suspicion of clinical rejection. There is no noninvasive test or biochemical marker in heart transplantation.

Secondly, the observation that, if there

is graft dysfunction in heart transplantation, it has an incredible adverse outcome with up to 40 percent mortality at six or 12 months. It is this observation of the importance of hemodynamic compromise which literally mandates and dictates our approach to surveillance biopsies in an attempt to find rejection as it's evolving to try and prevent the development of hemodynamic compromise.

It's not a function driven protocol or approach in heart transplantation, although many biopsies are driven by an apparent suspicion of a decrease in function.

Unfortunately, there is no stepwise progression. We can't wait until a patient exhibits hemodynamic compromise to initiate mycophenolate or any other type of therapy, because this is not a gradual increase in progressive risk.

As I've pointed out, 15 percent of the patients who develop hemodynamic compromise have essentially no evidence of histologic rejection on biopsy, either at grade zero or 1A. Similarly, in the large compendium of the cardiac transplant research database in now over 5,000 patients has shown consistently over time that up to 15 percent of all the patients treated for rejection have no histologic

evidence, only on clinical suspicion.

So it is an imperfect system. It is an evolving system, and surveillance biopsies remain the standard, but they clearly, as we saw in some of the renal studies where it had traditionally been a function driven system, when they began doing protocol biopsies, found some histologic evidence that they would typically ascribe to rejection, and without treatment and no change in function those changes went away.

So we're dealing with seeing cells on the biopsy, interpreting that as rejection, and perhaps leads to an over-interpretation of the biopsy findings. We're also cognizant, however, of the morbidity associated with using enhanced immunosuppressive or pulse therapy, and so we are reluctant and try to avoid overtreatment; but, clearly, the state of the art in heart transplantation is the combined approach to both biopsy proven and clinical suspicion, the so called treated rejection endpoint.

This data was just recently published, and it certainly brings home the point now in this very large series from the research database involving over 4,000 patients and some 3300 episodes of rejection

over this four-year period. It demonstrates the incredible importance and adverse outcome of a change in function in heart transplantation and why it is one of the most important endpoints for the clinician.

A patient who exhibits no hemodynamic rejection has a very good long and short term outcome. In contrast, very early after and usually associated with the development of significant hemodynamic compromise, there is a marked fall in survival; and this high mortality, which may be as much as 40 percent at six months and over 50 percent at two years, describes the impact and why we are so anxious about the possibility of a heart transplantation having a fall in function.

It is really the Achilles heel of heart transplantation, and I'll describe now the three most important aspects of the data.

One is the impact on rejection with hemodynamic compromise. It is, as I've tried to point out for you, the greatest cause of death. It dictates the needs and the approach to surveillance biopsies, and often requires very aggressive treatment with associated comorbidity. So a drug that may have an impact in this area would be a particular advance in the field.

Dr. Mamelok has alluded to the evolution or change in the protocol criteria used to define hemodynamic compromise. I want to reiterate that the initial design of the study was to describe criteria that might lead to initiation of treatment or therapy.

It was the first time -- There was no study that we could use as a benchmark or setting a precedent for criteria that could be used to define hemodynamic compromise, and so guided by trying to describe criteria to initiate therapy, we were perhaps too broad.

When the steering committee was presented with the data in a collapsed, totally blinded fashion, we saw a severalfold increase over what we expected to see, and realized that in our initial design we were too broad and too inclusive.

We then went to a criteria that we thought had the highest threshold to prove our suspicion of hemodynamic compromise; that is, the initiation of inotropic therapy or some clear measured assessment of ventricular dysfunction, which in this case describes about a 50 percent fall in function, pretty specific and objective criteria.

The bottom line for the patient or the practicing physician is very clearly made on this

slide. Regardless of that controversy, in the follow-up of the patients who had hemodynamic compromise, for the first time we see a drug that suggests it may have a very significant impact on reducing the survival associated with the development of hemodynamic compromise, both at six months and 12 months.

An outcome in the azathioprine based patients, particularly, pictured in green, very similar to that which I showed in the large azathioprine based cohort in the Mills study just published.

Secondly, the overall composite of the rejection findings in this study: Again, we looked at histologically proven and those clinically suspected as the composite endpoint. In the clinician's perspective the most important, the clinical practice treated rejection endpoint.

MMF had a significant -- or a marked impact on rejection in a progressive fashion of more effect with worsening biopsy grade; but I think most compelling, to me, was the consistency of the data.

If you look at the treated patient analysis of those patients who were treated for rejection, in the treated analysis there was a .06 p value -- .026 p value in favor of mycophenolate

reducing the incidence of treated rejection.

Similarly, although not all significant, there were certainly trends in favor of MMF in all of the endpoints, such as greater than 3A rejection, use of OKT-3 or hemodynamic compromise by the restrictive criteria. So a fairly consistent body of evidence of its impact on rejection in heart transplantation.

Finally, perhaps from a patient perspective this relatively unexpected finding: Many of the investigators in the field, including those who were on the steering committee and investigators in the study, were skeptical that we could ever show, despite OKT-3, triple therapy, many of the advance in the field -- we have not been able to demonstrate a change in survival.

We were very skeptical that we could ever show a change, and yet by Kaplan-Meier analysis at one year, this study did show a beneficial effect of mycophenolate in reducing the mortality associated with heart transplantation.

So for the first time, we had prospective data in a very well designed and executed study to show a survival benefit in heart transplantation. As Dr. Mamelok alluded, this benefit seemed to be immunologic related in that most of the deaths were

either due to rejection itself or to sepsis and severe infection.

We think that -- As I look at this data, it looks like it may be an agent that has some of its greatest impact in those patients which I defined as being at some of the highest risk, those with hemodynamic compromise or, worse, rejection.

So taken as a composite, the collective data, I think that we've shown that there is a very substantial experience in renal transplantation in three studies which showed a very consistent, nearly 50 percent reduction, in acute cellular rejection, and the cardiac study 1864 which showed in the treated patient analysis very favorable outcomes in rejection, hemodynamic compromise and survival, as well as a very good profile for safety and tolerability, again as outlined, with opportunistic infections largely relegated to relatively simply treated, and a near total lack of fungal infection or pneumocystis as an etiology.

So I think there is very consistent evidence of the efficacy and safety of this agent.

Finally, I would actually describe this as a landmark study. In the beginning it really accomplished very many things in the field of heart

transplantation. This trial was the first prospective, randomized, controlled trial to exist in heart transplantation, and stands to date as the only one, but perhaps equally importantly, because there had been no precedent and no trial of its design in heart transplantation, it established standards of care. It established new criteria for defining hemodynamic compromise, ways of caring for patients, thresholds to initiate rejection therapy, and so made a big advance in the field of heart transplantation.

I think, equally importantly, are the three analyses that I've described, the survival benefit associated with its use. For the first time, not a reciprocal relationship where you decrease rejection death, but by being so potent, you enhance infection death. This agent showed both a reduction in rejection death and infection death, and had a significant impact on one of the highest risks of mortality, that when there is significant graft dysfunction.

So I think, in summary, I would describe this agent and this study as having shown an agent that, I think, fills a very pressing and unmet need in the field of heart transplantation.

I'll turn the program back to Dr. Stempien

for closing comments.

DR. STEMPIEN: Thank you, Dr. Miller.

As we have heard, the mycophenolate cardiac study 1864 presented special challenges for us. There was a compelling ethical need to do an active controlled study, and mycophenolate was compared to the current standard of care, which is azathioprine containing triple therapy.

In terms of our primary endpoints, we did not meet one of the two primary endpoints based on the analysis of the enrolled population. Our hypothesis was that mycophenolate would be superior to azathioprine for the six month rejection endpoint, and in fact, no difference was found between the treatment groups for this endpoint, based on the enrolled analysis.

In this study, however, there are limitations in looking at the enrolled population. In retrospect, our study design randomized too early relative to the start of study drug, and we should have randomized when we were comfortable that the patients were ready to tolerate oral medication.

Because of this, we feel it is more appropriate to look at the treated population, and that this look is valid because the treatment

assignments in this group were made randomly.

We have briefly reviewed the established renal efficacy of mycophenolate, and we believe the data from the cardiac study taken in total support the efficacy of mycophenolate in preventing cardiac rejection and death.

Pre-specified analyses in the treated population show that mycophenolate is at least as effective as azathioprine, and suggests that mycophenolate may be superior to azathioprine, and Dr. Miller has given you his clinical perspective regarding the importance of these results.

Mycophenolate represents an advance in cardiac transplant immunosuppression and should be approved for the prevention of rejection in cardiac transplant. Thank you.

That's the end of our presentation. We would be happy to take questions.

CHAIRMAN MASUR: Okay, thank you. Why don't we start around the table and see if there are questions. We could start with Dr. Pina and move up, if there are questions. Dr. Starling?

DR. STARLING: I have a couple of questions that are mainly related to the protocol. Shall I address them to you?

CHAIRMAN MASUR: You can address them to whichever speaker you would like to address them.

DR. STARLING: With regard to the protocol, were there -- were patients a priori excluded that were "high risk" from the standpoint of their PRA crossmatch, etcetera?

DR. MAMELOK: No.

DR. STARLING: Okay. Secondly, was there induction therapy used at all?

DR. MAMELOK: Induction therapy was used in about 22 percent of the patients in both groups. It was left up pretty much to the --

DR. STARLING: Okay, and as far as the patients with hemodynamic compromise, was there a threshold that was required as far as the cellular grade of rejection to fall into that group or could a 1A or 1B --

DR. MAMELOK: Any grade of rejection, 1A on up, would get you into that group.

DR. STARLING: Okay. Next question has to do with infection prophylaxis for CMV and HSV.

DR. MAMELOK: There was no specification whether patients needed to have prophylaxis or not. We didn't ask that specifically. We do have some information. We looked at that in an indirect way, so

to speak, by looking at how many patients received acyclovir or gancyclovir in the first 14 days post transplant.

I believe a little more than 50 percent received acyclovir, and a little less than a third received gancyclovir in the first 14 days. Some of that was probably for treatment, but some of it was probably for prophylaxis, but I can't differentiate the two.

CHAIRMAN MASUR: Was that balanced?

DR. MAMELOK: Yes.

CHAIRMAN MASUR: And there was no pneumocystis prophylaxis?

DR. MAMELOK: Well, again, there was no specification in the protocol that you either were allowed or not allowed to use prophylaxis, and patients -- Certainly, there were patients who received both pentamidine or trimethoprim-sulfa, and I presume some of that was, in fact, for pneumocystis prophylaxis, but it's difficult to tell who.

We also had some cases of pneumocystis as well. Again, the use of those agents was pretty balanced. There were more pneumocystis cases in the AZA group, but in terms of the use of the drugs, overall they look pretty balanced.

CHAIRMAN MASUR: Is there more cases of proven disease?

DR. MAMELOK: I guess it gets into how you define proven. Certainly, the infectious disease component of this protocol was not at the rigor that you would require if you were actually doing a study in any of those diseases, and the -- so opportunistic infections were collected as part of adverse event collection.

So if the site, you know, deemed that they felt the patient had pneumocystis, CMV, what have you, and they put that in an adverse event form, then they were counted in that group. I'm sure that, if that was subjected to the rigor of an infectious disease trial, that wouldn't hold up, but that's what we did in this trial.

CHAIRMAN MASUR: So in other words, there were no a priori definitions of your opportunistic infection endpoints?

DR. MAMELOK: Well, yes. There were definitions for some of them. For example, CMV was divided into viremia and tissue infection and disease, disease being patients who shed, were basically shedders in urine or sputum; and CMV infection required someone to write on an adverse event form,

you know, pneumocystis pneumonia, for example, but we didn't require them to provide the documentation that someone actually had pneumocystis pneumonia or CMV pneumonia. If they wrote it down, that's what we said they had, and then they were put in the tissue infection group.

Similarly, if CMV were isolated from blood, then they would be in the CMV viremia group.

DR. STARLING: Next question: Regarding the use of HMG-Co A reductase inhibitor, was that looked at and, if so, was that balanced in the treatment groups?

DR. MAMELOK: Yes, it was.

CHAIRMAN MASUR: Dr. Starling, can I ask you, since all this is recorded, you won't get your per diem unless you speak into the mike.

DR. STARLING: I'll repeat the question.

The question had to do with the use of statins or HMG-CoA reductate inhibitors. Was it recorded, and was it balanced between the two groups?

DR. MAMELOK: Yes, it was recorded. If I could have Slide CM-8, please.

This shows the distribution of statins, and I think you would say they were balanced.

DR. STARLING: Okay. The next question I

have is: In the -- Specifically, in the patients that died with hemodynamic compromise, I believe it was 12 patients that were in the azathioprine group, and zero in the MMF group.

Were there any differences in those specific patients as to how they were treated, the use of OKT-3, ATgam, etcetera?

DR. MAMELOK: I don't think I can actually answer that. I don't know the specific therapies that they got at the time.

DR. STARLING: Okay. Thank you.

DR. MAMELOK: Dr. Miller reminded me that, actually, when those criteria are used as guiding therapy, if someone had hemodynamic compromise, then they were required to get OKT-3 or ATG.

DR. STARLING: So all the patients that fell under that category would have received OKT-3 or ATgan?

DR. MAMELOK: Yes.

DR. PINA: I have a question in your slide number 62 where you show the rejection rates at six months by IHSLT grade.

On the y axis you have percent of patients. Is that percent of patients who rejected or percent of patients who were treated?

DR. MAMELOK: That's slide 62 from the presentation?

DR. PINA: Right.

DR. MAMELOK: Could we have that slide up?

DR. PINA: Main presentation.

DR. MAMELOK: Yes. Is this the slide you're referring to?

DR. PINA: Right.

DR. MAMELOK: Yes. The percent -- For each panel we looked at, you know, the full group. So there are the total patients in the biopsy grade 1, that 97 percent of 289 for AZA, and 95 percent of 289 for MMF; similarly, at grade 2 at 69 percent of the 289 for AZA, and 65 percent of the 289 for MMF.

DR. PINA: So in other words, approximately 45-53 percent of patients enrolled had at least a grade 1, grade 3 or higher rejection?

DR. MAMELOK: That's correct.

CHAIRMAN MASUR: Dr. Starling, another question?

DR. STARLING: No.

CHAIRMAN MASUR: Dr. Griffith:

DR. GRIFFITH: Dr. Mamelok, I wonder if you could clarify for me the question that I asked earlier. That is, of the 11 percent dropout rate or

72 people, you said that 74 percent of those patients received azathioprine.

What was the outcome in that group?

DR. MAMELOK: Actually, first of all, the patients -- Well, when you say what was the outcome, you mean in terms of -- I mean, the outcome was for the whole group given -- you know, at six months for rejection and mortality at one year.

DR. GRIFFITH: Yes.

DR. MAMELOK: So you're --

DR. GRIFFITH: I'm asking you, did you follow the endpoints for that group?

DR. MAMELOK: I'm sorry? Yes, we followed the endpoints. In the treated group, once you got one dose of study drug, you were followed for the full six months, whether you were still on study drug or not, for rejection; and for a full year --

DR. GRIFFITH: That's not the question. That's my second question.

DR. MAMELOK: Oh, you're looking for the outcome in the patients who never received study drug. Oh, I'm sorry.

Could we have that module -- If we could have ET-19, please.

First of all, this just basically gives

you the reasons that patients withdrew from the trial, as defined on the cases -- All these cases were reviewed, and it turns out most of them couldn't get study drug, for one variety or another, because they couldn't take oral medication, and sorted out into these categories.

If I could have ET-20: This is the survival curves with the mycophenolate, I guess, in changing color from green to blue, and the AZA patients in orange. You can see that there is a difference in mortality that occurs. Most of the difference, actually, occurs in the first 21 days, and then the lines tend to be parallel.

DR. WOODLE: Can you tell us -- 74 percent of all the untreated patients received AZA. What percentages in the MMF and in the AZA groups actually got AZA?

DR. MAMELOK: Well, when they were in the active part of the study, they got what they were assigned to. So the MMF patients didn't get any AZA when they were still on study drug, and the AZA patients didn't get any MMF when they were still on study drug.

For patients who withdrew from the trial and then -- So when they were taken off study drug and

then were treated, you know, basically, per whatever physicians wanted to treat them with, about two-thirds of them -- two-thirds of the AZA patients continued to get AZA, and two-thirds of the MMF randomized patients, when they withdrew from the trial, were then put on azathioprine; but when they're on study drug, while they're still active in the trial, they're getting whatever their assigned drug was.

DR. WOODLE: But if they're untreated, they never got study drug.

DR. MAMELOK: If they're untreated, then they never got study drug.

DR. WOODLE: So the question is: Of the untreated patients, those that were MMF assigned, what percentage of those got AZA subsequently?

DR. MAMELOK: Of the untreated?

DR. WOODLE: And of the AZA assigned that were untreated, what percentage of them got AZA subsequently?

DR. MAMELOK: I think I can get those numbers for you. It was about equally distributed.

DR. WOODLE: In the untreated groups, there's a worse survival in the MMF assigned patients than there is in the AZA patients. The question is: Is there a difference in those two groups in whether

or not they got AZA subsequently?

DR. MAMELOK: Right. If I could have that slide up, please.

This shows in the 34 patients who were assigned to azathioprine, 19 got azathioprine. Of the 38 who were assigned to MMF, 15 got azathioprine.

CHAIRMAN MASUR: We'll come back as we go around.

DR. MAMELOK: Take this slide off.

CHAIRMAN MASUR: Bartley -- Steve, do you have follow-up on that or should we go back to Bartley again? We'll come around so we can get to everybody.

Bartley, do you have other issues?

DR. GRIFFITH: Yes. Not issues, just questions.

I wondered about the change in hemodynamic compromise definition, and what it was in the original protocol that seemed to result in a greater than 30 percent inclusion rate, which, admittedly, was a little high. What of those softer signs seem to be most problematic? Was it PA saturation or was it wedge pressure?

Do you have any information that could explain the difference between the ultimate severe hemodynamic compromise definition and the more

inclusive earlier one?

DR. MAMELOK: Yes. Could I have slide -- I could show this to you in two ways. first, let me see slide RJ-29, please.

This shows the various criteria for severe hemodynamic compromise with the treatment groups combined, showing you how many patients had each of the criteria. These are not mutually exclusive, because a patient could possibly have more than one criteria, but I think the ones that gave us the most problems in terms of the kinds of things you've asked were the S3 gallop in terms of being somewhat subjective and probably difficult, and the pulmonary capillary wedge pressure.

These patients were not necessarily required to have symptoms when they had these.

DR. GRIFFITH: Were there criteria for starting inotropic support?

DR. MAMELOK: There were no criteria for starting inotropic support specified in the protocol. That was left up to the clinical judgment of the investigators.

DR. KOBASHIGAWA: Jon Kobashigawa, transplant cardiologist. As the Chairperson for the mycophenolate multi-center study, I just want to add

some comments in regards to hemodynamic compromise and how the steering committee handled the definition.

I think that is one of the largest stumbling blocks. When we first began the study, we wanted to have some criteria where we could include patients to be treated without having histologic evidence for rejection. So we made this criteria for hemodynamic compromise rather broad, so that the clinician would have that variability to enroll that patient into the treated group, so we could treat that patient if we felt it was clinically indicated.

That's why the criteria was broad, but as Dr. Miller pointed out, transplantation in hearts is still evolving. As the years and not so many years went by, we began to note that hemodynamic rejection was something more narrow, more specific in terms of symptom generated as opposed to a protocol biopsy, and there was a big difference between that.

That's why we eventually revised the criteria to include hemodynamic compromise generated by the patient symptoms presenting, for example, with shortness of breath or with hypotension. That would be to the principal investigator's discretion to start inotropes on that basis to support blood pressure, support the hemodynamics.

We know that down to inotropes and to cardiac dysfunction, and that was evidenced by echocardiographic dysfunction, ejection fraction, decrease in fraction with shortening decrease, and we felt that this would reflect a more biologic representation of hemodynamic compromise, and that's where we evolved.

Even today, though, we may even change our definition of hemodynamic compromise as we evolve again into a more revised and more biologic, again, criteria, but this is how we are continuing to evolve in heart transplantation today.

DR. MILLER: One follow-up point, Bart, is that several of the centers have traditionally done hemodynamic monitoring at the time of every heart biopsy, regardless if driven by clinical symptoms. So the inclusion of finding a mixed venous sat less than 60 percent which could be driven by anemia and a variety of other factors still put them into the criteria which would typically potentially trigger treatment.

I think that may be one of the other major factors of why the incidence was so high.

DR. GRIFFITH: Thank you. Just a last question would be: Do you have any autopsy

information on the patients that died? Is there any difference in the histopathologic examination of the heart relative to the two groups?

DR. MAMELOK: Unfortunately, we don't have autopsy information on most of the patients who died. This is a shortcoming, I think, of this trial, and I think, unfortunately, of a lot of medical practice these days.

So I can't really give you, you know, real good -- I can't really give you comparisons in terms of what was seen by the heart, because the sampling is really not very broad.

I can give you ideas of what were found. Some patients, for example, had active rejection, active acute rejection. There were some patients who had transplant cardiovasculopathy. Some patients had -- There were a few patients who had evidence of myocardial infarction. There were some patients who clearly died of infection.

So it's a variety of things, but in terms of -- We didn't really have enough organized and well collected autopsy information.

CHAIRMAN MASUR: Randall?

DR. STARLING: I just would make a follow-up question and comment related to the issue of

hemodynamic compromise.

Those of us who work in the field know that rejection is, obviously, a continuum that transcends from typical histologic cellular rejection to the issue of antibody mediated rejection to coronary vasculopathy. I'm sure that a lot of this initiation of treatment in the presence of "hemodynamic compromise" with a low grade cellular rejection is driven by the presumption that there are other factors in play, antibody mediated coronary vasculopathy, etcetera.

My question is: Do we have any data or insight into these particular patients as to the intervascular ultrasound findings and what was going on in the coronary arteries in the patients with hemodynamic compromise without "significant" cellular rejection?

DR. MAMELOK: I just want to clarify the question. Are you specifically interested in those findings in the patients who had hemodynamic compromise or in general across the board, because I think it is the latter, but --

DR. STARLING: In particular, the patients with hemodynamic compromise.

DR. MAMELOK: No, I don't have data

organized or collected in that fashion. A lot of them, of course, when they were having it, weren't having those kind of studies done.

DR. STARLING: I just -- I don't think that that knowledge particularly impacts any conclusions one would draw, but I think it just gives us insight from a pathophysiologic standpoint.

CHAIRMAN MASUR: Okay. Steve?

DR. PIANTADOSI: Thanks. The sponsors made me fairly uncomfortable with the repeated assertion that the treated patient analysis is valid because patients were randomly assigned to their treatments. This is simply not true, particularly in such a subset.

The issue is selection bias, and that selection bias could operate either on the patients who were selected for comparison or selection bias could operate on the patients who were excluded from the comparison. It's the latter that's of concern here.

In fact, we'll see in a second, there's some evidence for some very strong selection biases in the data that you've presented, but my first question, in particular, is: What are the general characteristics of the patients who did not receive

study drug, not so much in terms of what they ultimately received, but in terms of what their baseline prognostic factors were?

DR. MAMELOK: So the question regarding baseline is you're interested in some of the baseline characteristics.

We can go through some of those. Could I have that slide, please? This shows their age, and probably I can short circuit this in the sense that the characteristics that I presented for the treated group that we looked at were all balanced with one exception, and that was a cold ischemic time.

The mean cold ischemic time in the mycophenolate patients was 3.7 hours, and it was 3 hours or 3.1 hours in the AZA assigned patients. So there was a difference in cold ischemic time.

When we actually looked at the causes of death in the untreated patients -- if I could have ET-21, please -- there were 11 deaths in the AZA group and 19 in the MMF in the first 21 days, which is where that difference occurred, and the causes are about the same except for this category of "other."

Could I then have ET-22, please? In the category "other," there are a variety of terms that were used to describe what happened, but we've divided

them here into those that basically fit into the category of acute graft failure and then those that fit into some other category.

You can see, the difference in the "other" and, I think, the difference in causes of death -- the difference in incidence of death is explained by many more patients -- one, two, five, six, seven patients in the MMF group -- having acute graft failure compared to one in the AZA group.

It's possible that the longer average cold ischemic time was a factor in this, but because these patients were withdrawn from the trial without knowledge of study drug, we consider these to be randomly distributed events.

DR. PIANTADOSI: Well, I'm not so sure that I would, but we could come back to that later.

DR. MAMELOK: If we could just -- I think it's important for us to address the issue of whether the treated group -- The treated group at the top level, the 289 patients in each group, are indeed -- do indeed have their treatment assignments remain random, and I'd like to ask Dr. Koch to comment on that, please.

DR. KOCH: Let me try one, if there's less echo.

The concern that you express is certainly a concern that anyone looking at the study would have. My understanding is that the issue of treated or not corresponds to essentially an entry requirement. In order to be treated, patients had to be able to take oral medication.

So this is not a situation where a patient had been assigned and one used treatment, and then made the decision to apply the treatment on the basis of a characteristic. If the patient didn't fulfill the entry requirement in order to get treatment, then they didn't get treatment.

It is in that sense that the decision is made without any knowledge of treatment and, hence, is a decision that applies without any bias with respect to the originally assigned treatment.

On that basis, then one simply then makes the argument that the treated population is as randomized as the original population was.

Now the sponsor did do a variety of analyses to evaluate distributions of baseline characteristics and found, for the most part, that baseline characteristics were distributed similarly for the two arms in the treated population, with perhaps one or two exceptions that would be consistent

with chance in the usual sense.

Also for the death or retransplantation endpoint, they did analyses that adjusted for a wide range of baseline characteristics, and on that endpoint in a proportional hazards model they found essentially the p value for death or retransplantation as they presented for an unadjusted analysis here.

DR. PIANTADOSI: I'm not disagreeing with the argument or the data as presented or the manipulations of the data. I am disagreeing with the conclusion, however, and what I'm really driving at -- the point of the question is whether there's evidence of differential selection in the two groups, and I think there is, and I think you've shown it twice now.

Could we go back to the Kaplan-Meier curve that you showed for a second?

DR. MAMELOK: Sure. When you say you disagree with the conclusion, which conclusion are you particularly disagreeing with?

DR. PIANTADOSI: Well, you said repeatedly that the treated patient analysis is valid, because the assignments were made randomly. I think, actually, strictly speaking, that's not correct, and it boils down to whether there is selection bias in the subset of patients that was excluded.

I'd like to look at the Kaplan-Meier curve again, because I think there's some evidence for it there.

DR. MAMELOK: That's in the untreated patients?

DR. PIANTADOSI: Yes.

CHAIRMAN MASUR: Actually, Larry wants to ask one question as part of that.

DR. HUNSICKER: Actually, what I want to suggest is, for Les Miller's sake, that I think this particular discussion is likely to take a rather longer period of time. I myself have a lot of questions, and these don't really involve Les, particularly.

What I should like to ask, if Dr. -- Steve over there --

DR. PIANTADOSI: Piantadosi.

DR. HUNSICKER: -- is willing to do this, if we could put this discussion off until we have finished all of the clinical things that we want to extract out of Les.

DR. PIANTADOSI: That's fine, Mr. Chairman. I'll do that.

CHAIRMAN MASUR: We can do that although, again, we still have an hour and 15 minutes to discuss

this; but we can come back to this.

Steve, do you want to ask a question on this or shall we come back to the statistical issues later?

DR. SELF: Well, I have a question, and it's about this, but it's actually not a statistical question. It's a clinical one.

The untreated group -- a large percentage were treated, 74 percent. I was interested to see that, actually, a few of them were treated with MMF.

I wonder, clinically, that group of patients who aren't able to receive oral medication within the first five days, if MMF is approved for this use, would you propose using MMF after five days post-transplant for those patients who then become able to take oral medication?

DR. MAMELOK: No, I would recommend that oral mycophenolate be used within five days. I mean, some patients were able to start oral medication before five days. The average start time in the treated group was about two days, and well over 90 percent started -- about 95 percent started within the prescribed five days, and a few were a little later, but all within the first ten, but basically they all were in the first five.

So I think as soon as you can start oral mycophenolate is when we would recommend starting it.

DR. SELF: And if you can't start it within the five days, you would recommend going with AZA at the time that the patient is able to take oral medication?

DR. MAMELOK: I think I would defer that question to Dr. Kobashigawa.

DR. KOBASHIGAWA: Jon Kobashigawa. At the beginning of the study, we did not have intravenous formulation of mycophenolate. Now we do. So I think your question is well warranted, but now, since we do have IV mycophenolate available, we can administer it in that form.

We do so for azathioprine as well when we cannot give oral. We will give intravenous azathioprine and then start oral, and we do the same for cyclosporine and even -- sometimes given intravenously, again when those patients are not able to tolerate oral medications.

DR. STEMPIEN: Dr. Stempien. Just a clarification. While we do have an IV formulation and have submitted an NDA for that formulation that's currently under review, the IV formulation is not at this time available. However, we are hopeful that in

the future the IV might be applied to situations such as you describe.

DR. HUNSICKER: I would say that we have extensive experience with the use of mycophenolate in kidney transplantation. If you can't use it within the first five days, for one reason or another, you use it after the first five days. You use it when you have it available. So it is not something for which there is any evidence that it is essential that it be started within the first days.

DR. SELF: So if that's the case, then it seems to me, from a -- statistical issues aside, that group of patients who were untreated are clinically relevant. They do contribute to kind of the overall net picture for a patient undergoing cardiac transplant.

DR. HUNSICKER: I'd rather defer that discussion to when we get back.

CHAIRMAN MASUR: Okay. Darrell?

DR. ABERNETHY: You showed the data from the entire group, 323, 327, for death and mortality, and then for the selected group, 289, 289. For the rejection and hemodynamic compromise patients, we didn't see both sets of data.

I was hoping that we could see the data

for the entire group for rejection and that endpoint.

DR. MAMELOK: So you want the same specific data in the enrolled population?

DR. ABERNETHY: Right. Exactly.

DR. MAMELOK: Sure. If I could have -- I'll find it for you in just a second. It may be in a slightly different format, but I think it will be the same data. Could I have slide RJ-7, please?

This is the data in the enrolled population for grade 1A rejection. Similarly, most patients have it, and there really is not a difference.

Then could I have RJ-37? No, I'm sorry. It's proving Grade 2 in the enrolled.

DR. ABERNETHY: I guess I was hoping we could see the comparable Kaplan-Meier curve.

DR. MAMELOK: Oh, the Kaplan-Meier curve for rejection?

DR. ABERNETHY: Right.

DR. MAMELOK: Okay. The Kaplan-Meier curves for rejection -- If I could see RJ-46. That's treated. Sorry. May I have slide RJ-38.

Okay. This is a Kaplan-Meier curve for the grade 3 rejections in terms of their severity, and there's a trend along the curve after a month, of

course, but there's no statistical difference there.

DR. ABERNETHY: Then could we -- so we can refresh our memory -- compare that to the 289/289 group?

DR. MAMELOK: Okay, but you'd like to see Kaplan-Meier curve for that, because they didn't show a Kaplan-Meier curve for that. I think I can get you one, but if I could have RJ-46. So that's in the blue line mycophenolate. Orange is AZA.

DR. HUNSICKER: And that was also not statistically significant, since the --

DR. MAMELOK: That was .056.

DR. HUNSICKER: The Kaplan-Meier what do you call it --

DR. MAMELOK: Log rank test.

DR. HUNSICKER: -- the final test, the Mantel-Haenszel is not significant.

DR. MAMELOK: The CMH test -- it was a p of .05, but the test for the Kaplan-Meier curve, which is a different test -- Do we have that p value? This curve is not significant.

CHAIRMAN MASUR: Okay. Wafaa?

DR. EL-SADR: I have a couple of questions about -- You showed a lot of details about the patients who withdrew approval or did not take study

medication. Do you have data on the loss to follow-up in general amongst the two treatment arms, as well as also the duration of follow-up by treatment arm?

DR. MAMELOK: Yes. There were no patients lost to follow-up. The datasets for this at the six month rejection endpoint and the one-year mortality endpoint are complete. That is, we have information on all patients enrolled in the trial.

Your second question was -- Oh, how long a follow-up do we have?

DR. EL-SADR: I guess what I'm getting at is you showed data, for example, on mortality as a percent rather than rates of X death per X person years of follow-up, and it just -- That would take into account the varying periods of time that --

DR. MAMELOK: Well, all patients were followed -- For the mortality endpoint, the mortality rate at one year -- the denominators are the full denominators for the enrolled group. So in other words, all -- The rate we give is the percent of, you know, patients enrolled for the enrolled group, and the percent of patients in the treated group, and it's all of them. So -- and they're all followed for the same period of time.

So that every patient is followed for

mortality, for example, to one year. So we know at one year whether a patient is dead or alive, and then we can -- You know, then we calculate the rates. So those rates were not estimates. Those were rates based on the full group.

DR. EL-SADR: The other -- My last question is about the discontinuations for all reasons. You show discontinuations of study medication for adverse events. I assume there were -- In addition to, obviously, death, were there other reasons for discontinuation, and were they similar or different between the treatment groups?

DR. MAMELOK: There were some other reasons for patients discontinuing from the trial. If I could have ET-4, please.

This shows the various reasons for patients withdrawing from the trial. As you can see, the most frequent occurrence is adverse events, and then there are other reasons here. When you get down to the small percents, there are some differences, but they're relatively small.

DR. EL-SADR: My last question is the biopsies. I assume that there is also -- These were not blinded. I mean, the biopsy results went back to the investigators. Right?

DR. MAMELOK: Well, see, the biopsy result went back to the investigator for a patient, but they were blinded as to what therapy they were on, but they knew what the biopsy results were to, you know, modify the care of the patient.

DR. EL-SADR: Right. Could that have influenced -- I mean, there's a difference in the biopsy -- in the grades on biopsy of rejection. Could that have influenced -- I guess, getting back to the decision to initiate treatment for rejection?

DR. MAMELOK: The decision -- So you're asking whether the grade of biopsy influenced the decision to treat rejection?

DR. EL-SADR: Right.

DR. MAMELOK: Yes, it did. So, for example, if a patient with a mild -- Patients with grades 1 level biopsies without any signs or symptoms of anything were not, I don't believe, required to have treatment. For patients with grade 2 biopsies, those patients were in general treated with steroids, and for higher grades steroids or OKT-3 or ATG would be the typical regimen for treating rejection for those types of patients.

DR. EL-SADR: It was required by the protocol or was left up to the --

DR. MAMELOK: It was required by protocol, and then there were other patients -- There were some patients, however, who were treated as protocol exceptions for a variety of reasons.

CHAIRMAN MASUR: Is there any difference -- Has there been analysis of the histology of rejection between the two arms? Is the histology identical at each grade level in terms of the cell types, etcetera?

DR. MAMELOK: Well, to the degree that everybody was following the ISHLT grades of rejection, we did have -- Before the trial was initiated, all the study site pathologists were convened, and those criteria were reviewed by an expert cardiac pathologist, and then they were asked to follow those rejection definitions.

DR. HUNSICKER: There was a central review of refraction at the biopsies, and you could comment on whether the rejections seemed to be equally graded in the two arms, based on that central review.

DR. MAMELOK: Yes. As Dr. Hunsicker points out, we did have a central review of biopsies -- of a selection of biopsies on the patients to get an idea of how pathologists expert in the field, unassociated with the patients, would review the

biopsies compared to the study.

CHAIRMAN MASUR: So they're consistent. So there's no reason to think that the histology with one therapy was different from the histology --

DR. MAMELOK: That's correct. That's correct.

DR. PINA: I think, as a point of perhaps clarification, and having walked around with this appendix in my pocket for the time of the duration of the trial, investigators tried really to stick to the algorithm that's presented in your protocol, page 195, and I think it's a protocol page. It's Appendix E.

There was an attempt to be as consistent as possible, once the grade of rejection was returned, with or without hemodynamic compromise, the criterion having changed later on, to follow this very, very closely. If you look at this, this is not outside the general practice of what's done today for treatment of hemodynamically compromising rejection.

So I think that there was pretty much consistency in trying to follow this protocol, and it was pretty well laid out.

I also -- I have a question and a comment. On page 14 of the protocol it states that azathioprine could be administered open-label immediately prior to

transplant. I understand there was a group of patients who received cytolytic therapy at the time of transplantation, and this really varies from center to center as it's been done.

How many patients actually received azathioprine prior or at the time of transplant?

DR. MAMELOK: We're going to see if we -- I don't have that piece of information in my head. We're going to see if we can find it. As I indicated before, about 22 percent received cytolytic therapy, but for azathioprine we'll see if we can get that out of the database.

DR. PINA: Because for the panel's clarification, at the time that the patient gets called, most centers have a protocol to administer cyclosporine, a certain amount of steroids, and azathioprine open-label. So I think it would be of interest to see how many people received that.

CHAIRMAN MASUR: All right. Perhaps we'll come back to that. Steve?

DR. WOODLE: There's a reasonable cadre of people in renal transplantation now that believe that early loading of immunosuppressive agents -- that is, within the first 24-48 hours -- is essential for achieving the lowest rates of rejection.

One of the things that struck me about this trial was that patients were delayed in giving the test drug for few to several days, and the other interesting -- The other thing that's important to realize is that, when one starts mycophenolate, you may not get therapeutic levels or levels that you feel may be therapeutic for a few days afterwards.

So there may be a substantial number of patients in this trial that didn't have what we might consider to be an effective level for several days after transplant. So I had a couple of questions to try to get at that.

One is: When was the drug actually started, azathioprine and MMF? What were the mean times to starting drugs and median times?

DR. MAMELOK: The mean and median times were very close, and they're about two days in each arm.

In terms of the time it takes to reach therapeutic concentrations, I'm going to ask Dr. Nicholls, who is a clinical pharmacologist on the project, to address that question.

DR. NICHOLLS: Yes. I'm Andrew Nicholls.

There isn't, in the case of mycophenolate, any strong evidence on kinetic grounds to propose

loading doses. The pharmacokinetics very rapidly reach steady state. So essentially the pk profile on Day One, though it changes over a period of three months, looks very much like a pk profile on Day Two and Three and Four.

So for that reason, we wouldn't propose loading doses on pharmacokinetic grounds.

DR. WOODLE: Did you have a chance to look at the patients in terms of those that did experience rejection and those that didn't as to -- Was there any relationship to when the drug was actually started?

In other words, those in whom drug was started later -- were they at higher risk to experience a rejection episode or a more severe rejection episode?

DR. MAMELOK: No, we didn't do that analysis.

DR. ABERNETHY: I would follow up on that question about loading. What was the accumulation ratios from other studies? With the half-life this drug has, it seems like that the first dose will not get you to a steady state.

DR. NICHOLLS: Right. This question about half-life -- The half-life of this drug is a rather complex concept. When we look at the decay curve of

MPA concentration with time, it is, in fact, complicated by the influence of enterohepatic circulation.

So it's a rather -- The term half-life cannot strictly be called elimination.

DR. ABERNETHY: Right, but the simple thing to think about would be what's the accumulation ratio?

DR. NICHOLLS: Right. If you approach that by looking at pre-dose concentrations, to look there for evidence of an exponential, if you like, increase of pre-dose concentration -- as I mentioned, first day profile looks very much like the next day profile. There's really very little evidence of a gradual increase in pre-dose concentration with time.

DR. ABERNETHY: So the accumulation ratio after a week of dosing, for example, is 1.0. Is that what you're saying?

DR. NICHOLLS: It's very close to that indeed.

CHAIRMAN MASUR: Steve, other issues?

DR. WOODLE: Yes, just one other issue regarding the path review. The central path review was only on a subset of patients with hemodynamic compromise. Is that true?

DR. MAMELOK: Yes, that's right. We first identified patients who required treatment and had hemodynamic compromise by --

DR. WOODLE: But then it was just a subset of those. Right?

DR. MAMELOK: Then it was a randomized sample of that group, yes.

DR. WOODLE: What was the total number of patients or samples that were actually reviewed?

DR. MAMELOK: Well, when we did the randomization, there were 57 patients selected, and on five of them we could not actually get slides. So the actual review was done on 52.

DR. WOODLE: Were the individual pathologists at the institutions blinded to clinical data?

DR. MAMELOK: The individual pathologists -- The pathologists at the study sites, you mean?

DR. WOODLE: Yes.

DR. MAMELOK: They were not blinded to clinical data, no.

CHAIRMAN MASUR: Larry?

DR. HUNSICKER: I'm going to suggest that we take the advantage of Les' last hour to do a combined thing that's going to address both question

1 and question 2 that the FDA is putting to the panel.
2 So I'm going to perhaps ask the cardiologists who
3 represent the Roche group and also our own
4 cardiologists perhaps to comment on a series of
5 questions that I think that we perhaps want to get out
6 and discuss a little bit.
7 Before I do that, I want to say, possibly
8 because I will be somewhat critical of some of the
9 aspects of this study later on, that I want to say up
10 front that I recognize that this is unquestionably the
11 best done study in the area of cardiac transplantation
12 that's ever been done.
13 The investigators deserve a good deal of
14 congratulations for what they've accomplished. I also
15 want to say I have had the opportunity now to serve on
16 -- this is my fourth review board. Three of these
17 happen to have reviewed applications from Roche, and
18 I believe that Roche has really set a standard for the
19 conduct of clinical trials in the area of
20 transplantation, which all of us in the community
21 should be grateful for.
22 I say that, as I say, because I will be
23 critical of some aspects of the study later on, and I
24 don't want it to be lost that this is really an
25 extraordinarily important first step in the study of

cardiac transplantation.

Now I want to preface my comments -- the question that I'm going ask by a good deal -- by letting everybody who might not be aware of this, be aware of the difficulties in deciding what constitutes cardiac rejection.

We have clinical, and we have histological criteria. One of the realities is that you can find cellular infiltration in cardiac biopsies that are done on a protocol basis, as were done in this study, that probably do not mean rejection; but we have not yet learned how to distinguish those that mean rejection from those that don't.

This means then that a patient with a rather mild rejection, a 1A by the definition of the ISHLT, may not have rejection at all in any meaningful way. A very substantial fraction of patients with a Class 1 rejection get better with nothing at all, and probably do not really have rejection.

Now someday we may be able to distinguish these things, but we can't right now. This is manifested by the fact that, while there were 313 and 312 patients respectively in the treated groups who had a biopsy grade 1A or higher, only 241 and 226 respectively received any treatment at all.

Conversely, you can have a totally negative biopsy, and yet in many cases it is likely that there is rejection present. Again, this is evidenced by the fact that, while there were only 65 -- I'm sorry, 121 and 120 patients who met the co-primary endpoint of a rejection at any grade with hemodynamic compromise, there were more than that, 241 and 226, who received treatment.

So neither the clinical nor the histological diagnosis of rejection is particularly solid in the area of cardiac transplantation. This leads to an issue when you try to figure out what might be an endpoint or what should be an endpoint.

The relevance to this specific trial is that it would seem reasonable to try to pair out, if we could find a way to do it, those patients who were included in the primary endpoint who didn't even have rejection.

It is a meaningful and important question to the second thing, in that what we really need to do is to see if we can define rejection.

Now I would state at the outset that there is another distinction here to be made between rejection and severe rejection, and this study was set up as a study of any rejection episode.

When you look at any rejection episode and you don't find a difference in that primary outcome, and then you begin looking at subsets, you get into the major problem of subset analysis, and severe rejection would be a subset.

So in order to try to clarify this a little bit, what I'd like to do, first of all, is to ask the sponsors if they can tell us, what was the distribution of cardiac rejection grade amongst the patients who had hemodynamic compromise who qualified for the endpoint, so we can see whether it is reasonable to assume that any of these patients or some of these or what fraction of these patients might not actually have had rejection?

Can you tell us the distribution of grades of rejection in the patients who met your primary outcome? The grades within the patients who met your primary outcome.

DR. MAMELOK: The primary outcome defined in the protocol, right.

DR. HUNSICKER: The primary outcome of any hemodynamic compromise plus any rejection grade 1 or greater. I want to know the distribution of those grades.

DR. MAMELOK: Okay. I can give it to you

for both -- First, I'll give it to you in the treated group. If you want it in the enrolled, I can give you that, too.

So I'll go -- First I will tell you, for grade 1A in the AZA, it was 9.3 percent versus 8.7 percent in the MMF; or grade 1B, 4.8 percent in AZA, 5.2 percent in MMF; for grade 2, 6.2 percent AZA, 3.8 percent MMF; grade 3A, 7.6 percent AZA, 9 percent MMF; grade 3B, 2.8 percent AZA, 1.4 percent MMF; and for grade 4, .7 percent AZA, .3 percent MMF.

DR. HUNSICKER: So I realize that I'm putting myself out on a limb, but if one were to see where consensus lies, the general thought is that treatable rejection, going on grade alone, starts somewhere in the middle of 2. 1 without any hemodynamic compromise, even by the protocol, doesn't require treatment; 3 where there is fairly widespread myocyte necrosis clearly requires treatment. It is rejection. A fair number of 2s have piecemeal necrosis, and it's a sort of a who -- oh, I see that I have -- Dr. Pina down there agrees. This is the never-never land.

What you see here is that perhaps half of the patients had rejection grades in the area where, without hemodynamic compromise, there would be

substantial question amongst the cardiac community whether this really was clinical rejection, irrespective of what the grade was that was stated.

Now what I want to put to the group, the cardiologists on the panel and also to the other, is that if you have a rejection at any grade and have hemodynamic compromise as it was defined in this protocol, would you consider that to be now meeting the criteria for rejection or is this a reasonable thing?

This is basically where they started. They said that, if there was either fairly severe rejection or hemodynamic compromise, this would quality as rejection. I guess I'm asking: What is the reasonableness of this definition or, put the other way, is there any patient who had a rejection of any grade and had hemodynamic compromise who you would not proceed to treat, as was stipulated in the protocol?

DR. RENLUND: Dale Renlund, transplant cardiology, University of Utah.

I think that the vast majority of patients who would meet that criterion, that they have very low levels of infiltrate histologically -- so very low levels of histologic rejection but are markedly

hemodynamically compromised -- I would say that the majority of those are rejecting and that that's a reasonable endpoint.

I think that --

DR. HUNSICKER: You said fairly -- I can't remember quite what the word was, but marked hemodynamic compromise. We have the criteria that we have in the protocol. If a patient met those criteria and had a positive biopsy, even if it were a 1, let's say, would you just that this patient should be treated for rejection?

DR. RENLUND: Yes.

DR. HUNSICKER: is there a consensus amongst the folks over there, all three of the cardiologists from the sponsor are agreeing, and here at the table?

CHAIRMAN MASUR: Larry, are you asking as if there's hemodynamic compromise without another defined etiology and any level of rejection -- are you asking whether that would be treated?

DR. HUNSICKER: Yes. My question here is: Can we come, first of all, for the purposes of this study, decide whether the endpoint, as it was defined in the protocol, is a reasonable definition of rejection, not severe rejection but just rejection?

Secondly, can we then at the end of this time suggest that that's not an unreasonable definition for future studies, as requested by the FDA?

CHAIRMAN MASUR: Again, Larry, if I just, as a neophyte in the transplantation world -- Presumably, it takes some clinical judgment to decide whether a hemodynamic compromise is related to rejection or whether there's some other process?

DR. HUNSICKER: I think that that goes without saying. If you have a patient who has a clearcut other reason for -- as was said by one of the guys over there, if there is anemia and the patients have a high extraction rate, you know, you don't know what to make of it. So you have to put this into a broader clinical context.

DR. RENLUND: I think that -- I think the answer to your question still is that, even with an ISHLT grade zero or 1A or 1B, if that patient has an ejection fraction less than 30, a fractional shortening that's less than 25, and 20 percent or a drop of 25 percent and requires inotropes, I think that's rejection in the vast majority of cases and, therefore, should be treated.

DR. HUNSICKER: So we then would have for future discussion down the line really two

possibilities. One is that any grade or rejection with something defined as hemodynamic compromise would be an endpoint, and the other would be that we should just ignore the biopsy and say, if you've got hemodynamic compromise that requires treatment, that is rejection. Those would be two possibilities.

What I guess I'm trying to establish is that the definition that is in the protocol is not an unreasonable one. Granted that there is uncertainty in this field. The investigators came into this trial with a definition that was at least a reasonable definition for an endpoint.

DR. RENLUND: Yes, I believe so.

DR. HUNSICKER: And do the other members of the panel agree with that?

DR. MAMELOK: Before we go on with this, Dr. Hunsicker, I just want to clarify that we're all talking about the same definition. So you're asking them, I think, if a patient meets one of the criteria in the original definition of hemodynamic compromise such as pulmonary capillary wedge pressure being high, has a biopsy or even a negative biopsy but, let's say, a biopsy of 1 or 1A, would that patient be deemed to have significant rejection based on that criteria for hemodynamic compromise, for example, in the absence of

symptoms?

I think -- I just want to make sure that we're all answering the same question. So that I just want to ask Dale if he meant that, if a patient has a pulmonary capillary wedge pressure of 20, is asymptomatic and has a 1A or 1B rejection, is that hemodynamic compromise?

DR. RENLUND: I'm much less confident about that than the revised criteria that we adopted, but I think that a reasonable doc. might get quite worried that something is wrong.

DR. HUNSICKER: I think that there are two questions, and this can be considered somewhat separately. The first is: What kind of a recommendation might we make for future trial studies?

There, I think one would want to give the combined cardiologic expertise on all sides of this thing time to work out some of the fine points, because it may not be that the criteria we have are really tuned optimally; but for the first question, a major question is: Is it reasonable to have set up the criteria as they were defined in the protocol or were they, in fact, sufficiently flawed that we should look at an alternative set of criteria?

This really gets to the issue of multiple

testing. The only reason why one, I think, can justify substituting one -- a separate endpoint for the endpoint that was in the study is the discovery that the endpoint in the study was really -- does not define the outcome that you are looking for.

If it is reasonable to say that the definition in the protocol, which was any degree of rejection plus hemodynamic compromise according to those criteria, then I think we have to say that substitution of an alternative endpoint is now looking at a second question or a subset question and has to be understood that way as you look at the statistics.

That's really the two pieces of what I'm getting to. I've understood Dr. Renlund to say that, while he might not be confident across the board that a person who had elevated capillary wedge pressure and a borderline biopsy of 1A or 1B biopsy would necessarily need treatment, that many clinicians would be worried by that finding.

DR. RENLUND: I think I understand now, Dr. Hunsicker. I think that the criteria -- Let's say ISHLT 1A, 1B, high capillary wedge pressure, and that's it. What percent of those are truly rejecting? I think that percent is quite a lot lower than the one on the revised criteria.

I think that somebody who's got an ejection fraction less than 30 percent and low grade rejection, I think the vast majority of those are rejecting; whereas, one that has a high wedge pressure and low grade infiltrate, I think it's less likely that that's there. If I were to put a number, I'd say that it may be 50/50 on that group.

DR. HUNSICKER: So that's what I was trying to tease out. Although I have invited Les to comment, he has deferred to Dale, but that's okay with me, because they're both good cardiologists.

It may be that we will come to a different conclusion about what should be used as a criterion for this study because of what was defined, and what should be defined in the future.

I think then what I would summarize is that the criteria are not totally unreasonable as they are stated here, but there may be some wisdom for future studies at least in honing them in.

I'll tell you that I'm very, very uneasy about defining criteria anew after the first look, and you all must understand that. I think that is a very dangerous precedent to set. You probably wouldn't have looked at it anew if it had been significant the first time around.

DR. MAMELOK: Dr. Hunsicker, I just want to clarify in a sense, I guess, what Roche's position is on this, because I don't think -- We're not trying to claim that, based on the evidence that we have, that we've, in a sense, proven definitively the standard that we would all look for, that mycophenolate is absolutely superior to azathioprine for preventing rejection, pure and simple.

I think what we're trying to say is that, when you take the renal data that we know about where it clearly is superior, and when you take the vagaries of how to measure rejection, and when you look at rejection by a variety of means, whether that requires treatment, whether it's by ISHLT grade or what have you, that the data are all consistent in favor of mycophenolate.

What I think we're asking the committee is to make a judgment as to whether the bulk of that data taken as a whole at least suggests that there may be some differences. That's really the position, and that's what we're trying to get some judgment here, not that we think that these data fulfill a standard that we would all prefer to fulfill.

We also think that there may be ways of looking at that data that go beyond just the nominal

p values that we gave, because as I think you've hinted at and heard you discuss at other times, because we didn't pre-specify the method as to which -- or the way we would actually evaluate those p values, it does present some problems, but we do believe that there are methods that allow you to at least assess those endpoints as a whole.

CHAIRMAN MASUR: Bart, you had a comment?

DR. GRIFFITH: Yes. I just -- I guess I wanted to speak to the issue that Larry is hammering at. I can just tell you that it's incredibly difficult to tease out this rejection issue. I mean, the easiest thing is death.

Dr. Starling and I were just saying, well, you know, alive or dead, everybody goes home, no question, you know; but this issue of rejection in heart transplantation is extraordinarily difficult.

I think this group really should be complimented, not castigated, because of their attempt in an unblinded -- in a blinded sort of way, when they realized that their inclusion criteria for hemodynamic compromise was too broad.

I think that that was a mistake in the beginning, because wedge pressure can just be a volume status indicator and really have absolutely nothing to

do with "rejection hemodynamic compromise." So perhaps the initial protocol team was a little bit less focused, but they did recognize that as a problem.

What they're trying to give us, the panel, is rejection that we consider as a cardiac transplant community to be the most devastating. That is, forget the scale or the grade, because that's biopsy dependent, and it's variable, depending upon where your forceps bites, and that's well known that you can miss biopsies that are very significant.

They're trying to link some tissue diagnosis with what we know now hemodynamically, severe compromise, as being the most ominous sign for death in this particular group of transplant recipients.

So I'm less uncomfortable with it. In fact, I kind of applaud it, although I'm not a -- I don't make a science of panels, and this, admittedly, is my first panel, but I kind of like the way they looked at this and said, whoa, we're way out of line here in terms of a 30 percent incidence of hemodynamic compromise, and let's take a look at that original group; because, in fact, they're giving us a better evaluation of their data by having done that.

DR. HUNSICKER: Just a comment, that I entirely agree with Bart's comments about applause to the group. I think that it's critical that they've gone through this exercise.

Having said that, I will say that, as a person who does, to some extent, make a science out of clinical trials, that I am very uneasy about relooking at an endpoint once it's been looked at.

CHAIRMAN MASUR: We'll come back to this. Susan?

MS. COHEN: I should say I'm a pinchhitter. I really am on the Derm and Ophthalmic board. So I'm getting a lot of experience on different boards.

Of that number, 578, you included some that only took one dose, if I understand correctly. Well, where do they fit in all the information? Did you separate out -- How many actually only received one dose of the 578?

DR. MAMELOK: Well, to answer the second part of your question first, I think -- and then maybe to ask you a question back, in a sense.

The point of including in the treated group of looking at patients who received one dose or more is simply -- In the ideal world we would have

been looking at the enrolled population. They would have all gotten study drug, and in that group we would have analyzed all patients, whether they got one drug or no drug or more.

So the issue we're faced here with was certainly unanticipated in that we had 11 percent of patients who got no study drug. So then, because of the reasons I described earlier, we thought it appropriate to look at the treated group.

Once we did that, though, we wanted to be sure that we analyzed every patient in that group, and I don't want to use words incorrectly or to cause more controversy maybe than I should, because we've had discussions with the agency about what's the best way to use -- what's the best terms to use here; but there's -- If I'm telling you what you know, please just stop me, and I'll just stop -- but that there's this principle of so called intent to treat.

What that means is that, if you have a randomized trial, you analyze everyone in the trial, no matter what they got, no matter what happened to them, etcetera. So what we've attempted to do in the treated group is at least apply those principles to intent to treat, once we've defined the treated population. So that's the reason for analyzing

patients, whether they got one or none.

We recognize that that's not -- that in the true absolute sense of the word, what intent to treat would be would be everybody in the enrolled population, but I'm curious. I'm not quite sure I understand the question that you were getting at about why we analyzed --

MS. COHEN: Well, if some only received one dose, how do you base a clinical trial on that, and how many did only receive one dose, because you're quoting 578, and that's your patient population; but I wouldn't want to be a patient to take the drug if there were several who only had one dose, and that's what we're basing it on.

DR. MAMELOK: No. If everybody got one dose or anywhere close to that, I would agree with you. Could I have that slide up, please.

I can't tell you exactly how many doses are here, but what this tells you --

MS. COHEN: You won't get paid, if you don't use the mike.

DR. MAMELOK: I don't think I'll get paid by the FDA.

There are eight percent and six percent of patients who got two weeks or less of treatment. So

the most those patients could have gotten would be 14 days of dosing or 28 doses.

Then another six percent got two to one month. Fifteen and 10 percent got one to six months. Thirteen and nine percent got six to 12 months, and the majority of patients got more than one year of therapy.

So there's a distribution here of lengths of time patients actually got dose.

MS. COHEN: What do you think of that as clinically significant, one to six months, or do you think weeks are clinically significant?

DR. MAMELOK: I guess there are two issues here. One is sort of trial methodology, and in terms of the trial methodology we would look at all of them. In terms of what would be clinically significant -- I mean, obviously, if you have a drug that you think works, that you would want to continue to treat patients with as long as you felt it provided benefit.

MS. COHEN: But if those one-dose or two weeks, etcetera, were successful, but then they dropped out, how does it affect the graphs that you draw? I mean --

DR. MAMELOK: I think it's fair to say that the patients who received therapy for these

truncated periods of time -- for one reason or another, you would say the drug wasn't successful. Either the patients died or they developed an adverse event so that they couldn't tolerate what therapy they were on, or a small number decided I don't want to be in a clinical trial anymore, something of that nature.

So I think it's a relatively safe assumption that the patients who were treated for two weeks or less in one way or another weren't getting benefit from the drug they were on in that short time frame.

DR. HUNSICKER: It might help Ms. Cohen to know that the majority of acute rejection episodes occur within the first three months. So that if people take drug for three months, it should be possible to evaluate the impact on at least the bulk of the rejection episodes.

Obviously, for one-year survival you would like to have them on it for as much as possible, but for the rejection thing it would probably suffice if they were most of them on for three months and, as you saw from the thing there, the large majority of patients were on at least for the first three months.

MS. COHEN: You used 28 centers. Were these major heart centers across the United States or

were they typical of heart centers that people could go to in any particular area?

DR. MAMELOK: No. They were centers all of which had active transplant programs.

MS. COHEN: All right, and did you compare one center to the other after you got the results of the trials? I would be curious to know how one center, in comparing them, if you found more problems in one center or another, more rejection, whatever.

I think it's important to know exactly from center to center, if the protocol was supposed to be the same, the end results.

DR. MAMELOK: Well, what we do -- The numbers of patients at any one center are relatively small relative to the whole. So, for example, in the treated group the most a center had was eight percent of the patients in the whole trial, and most of them had somewhere between one and three percent of patients in the whole trial.

We typically, and have done an analysis to see whether there are interactions by center to look at whether the results are consistent across centers, and looking at it that way, which is a standard statistical way of looking at it, there were no center interactions.

Of course, if you look at anyone individual center, you'll see, you know, results are somewhat different in each individual center, but those are based on small numbers. So there's a way to look at that effect on the whole, and there were no center interactions.

MS. COHEN: No, but patients do look, and you see written up all the time which centers do the most successful surgery. So, obviously, you want to pick the center that's had the most success.

DR. MAMELOK: Right. So I would ask Dr. Griffith to comment on that probably.

MS. COHEN: I have another question. I looked at your demographics, and you had 84 percent male. Does that mean that women don't get transplants? It's a very -- I mean, compared to -- I thought after the Framingham study, we decided that women should be included in studies.

DR. MAMELOK: Women were definitely included in the study. There was not a criteria to exclude women. Typically, in large databases -- The percent of patients who are being transplanted here split out by sex are pretty typical of what you find in large databases, and probably reflective more of the sex differences in patients getting cardiac

disease that lead to the need for transplant rather than discrimination against women.

MS. COHEN: And what about the 86 percent Caucasians? Multi-racial people have different heart problems or more or how did you determine to have 86 percent Caucasian?

DR. MAMELOK: We didn't determine it. Again, race was not an exclusion or inclusion criterion in the trial, and I think again the distribution by race is pretty typical of what we see in the transplant population.

Dr. Miller, I think, who has experience in this group, could probably comment on that.

DR. MILLER: If you look at the demographics from both the United States UNOS databases and the international, it's an observation that goes for 20 years that almost exactly 80 percent of the patients transplanted are male, and the Caucasian percentage is almost exactly what we see in this study. So it's very representative of the trends.

I think Dr. Mamelok has alluded to some of this, that if the age cutoff is roughly in the range of early sixties, the incidence of cardiovascular disease accelerates dramatically thereafter as the

protective effects of estrogens are gone. So that's part of the explanation, but these demographics are exactly what you would see for a long period of time.

MS. COHEN: Could it possibly be based on socioeconomic problems within the community, that some people -- these things are not available to them?

DR. MILLER: Certainly, that may play a role in the access to health care in general, but I think it's pretty uniform across the United States.

MS. COHEN: Well, I think that it might encourage people maybe if enough publicity was done about these things that people could learn more and see better help.

DR. STARLING: There are socioeconomics related to religious preferences, as far as organ donation and acceptance of transplanted organs that affects some of those populations, but --

MS. COHEN: I come from that group, but I would take them, believe me.

DR. STARLING: But I would echo, if you looked at three large heart transplant centers such as Pittsburgh, Cleveland Clinic, Temple, you would see that the demographics at those individual centers are very in line with what's presented in this information.

DR. PINA: Just as a comment, I echo what Les was saying about the presentation of women with heart disease occurs at an older age when most centers have already had a cutoff of age for transplantation.

The issue of socioeconomic is a very, very big issue, and when you get into the levels of Medicaid which is so state specific, it is sometimes very difficult to get these patients approved for coverage, and coverage may include not only in-patient coverage but also out-patient coverage.

There may be some patients who may have coverage for the surgery, but then when you turn to them and you tell them about their medications after transplant, which are horrendously expensive, they can either not afford it nor may have the coverage for out-patient medication. So socioeconomic issues are very, very real and present.

MS. COHEN: In a perfect world, we'd like to think, therefore, that companies would make available all kinds of drugs available to people who cannot get medication through Medicare.

MS. PINA: And they do, and companies do have these programs for indigent patients, but it's not always the expected medicines that we give them, the triple drug therapy. it's often other things that

present themselves, like antibiotics, which may be needed for extended periods of time.

CHAIRMAN MASUR: Wafaa, you had a question?

DR. EL-SADR: Yes. I had a question. Did you do strictly an on-treatment analysis? You did in the treated group, but you didn't -- but that's not really an on-treatment analysis.

DR. MAMELOK: Could you define for me what you mean by on-treatment?

DR. EL-SADR: Well, receiving study assigned treatment.

DR. MAMELOK: The treated analysis is the group of patients that received the study drug.

DR. EL-SADR: No, but that -- If you discontinued for AEs or discontinued for whatever, you still remained in that analysis.

DR. MAMELOK: Oh, okay. So you mean the event rate while patients were still on study drug?

DR. EL-SADR: Assigned study drug.

DR. MAMELOK: In the -- I have that for the mortality endpoint. In the mortality endpoint while on study drug, there were 15 deaths -- I'm sorry. Yes, 15 deaths in the azathioprine group and 12 deaths on the mycophenolate group.

We don't have the on-treatment for rejection, but that's the data for mortality.

DR. EL-SADR: And I assume that people could switch from MMF to azathioprine.

DR. MAMELOK: When they come off the trial, and in fact they did. About two-thirds of the patients who were randomized to MMF who came off the trial and then subsequently received immunosuppressive maintenance therapy were put on azathioprine.

CHAIRMAN MASUR: I had a couple of final questions. On your presentation slide 60, you showed in the treated group there's a dramatic difference in survival in azathioprine and MMF group. You showed us the cause of death to the population in general.

For the 32 percent versus zero percent in those with hemodynamic compromise, do you have any indication of what the cause of death in that azathioprine group was?

DR. MAMELOK: In the whole -- I'm sorry.

CHAIRMAN MASUR: Well, your slide 60, if you look at those who had rejection and severe hemodynamic compromise, there was a large apparent difference in those who got the two arms. What was the cause of death in those who got the azathioprine?

DR. MAMELOK: I don't have a slide broken

out by that. He's not asking for the cause of death in the treated group. He's asking for the causes of death in the 12 patients who died with severe hemodynamic compromise. I don't have it broken out by those patients.

CHAIRMAN MASUR: All right. An issue related to safety: Some of your preclinical toxicity assays suggested that there was nausea, vomiting, diarrhea. You showed in your AEs there weren't any substantial differences in the incidence of specific toxicities, but what about in terms of using antiemetics and antidiarrheal drugs? Was there a difference in your two arms?

DR. MAMELOK: In general, there was not a big difference for concomitant medications in general and for those in particular. If you'd like a particular percent, that will take me a little bit of time to get out of the tables, but they were about equal.

The difference in adverse events of diarrhea, for example -- There was about a nine percent difference between the AZA group and the MMF group, and when you look at severe diarrhea, the percents were low, about two percent in each group, and they were very close.

The same for patients actually discontinuing for diarrhea were very close within the two groups.

CHAIRMAN MASUR: Bartley?

DR. GRIFFITH: Yes, just a simple question. How did you handle the problem of dropping white count in one arm where you could reduce the azathioprine dose, presumably, from anywhere between 3 and 1.5, and then a locked-in dose of MMF?

DR. MAMELOK: You were also allowed to reduce the dose of -- Of course, you didn't know what you were reducing, but in either arm, if someone was dropping white count and you wanted to adjust the dose, you basically adjusted the dose for either, as you saw fit, and both dropped.

DR. GRIFFITH: Thank you.

CHAIRMAN MASUR: All right, Doctor -- One more question?

DR. HUNSICKER: Yes. Dr. Mamelok, I've been sitting here stewing over your last comments at the end of our section, and I want to ask you again to state for us what you think you have proved about the rejection part of this.

Specifically, I'm referring to your comments that sounded to me something like we are not

trying to assert that this would meet the usual criteria of having proved superiority but that there was a trend in that direction. Could you tell me precisely what you think you've established?

DR. MAMELOK: Yes. I think what we have established with the data that I've shown you is that MMF is at least as good as azathioprine for preventing rejection, and I think that we've shown you data that suggest that it may be better.

I would couch that both in the context within the cardiac trial and building on the information we have in the renal trial where the definition of rejection is much better defined.

I would also just like to ask Dr. Koch to comment on analyzing the multiple rejection endpoints, because we do recognize there's a problem there in terms of those p values.

DR. KOCH: You had made some comments earlier in reference to the attractiveness of the primary endpoint, and you asked cardiology colleagues whether or not it was a reasonable endpoint, and they agreed that it was; but you didn't ask whether it was a universally dominant endpoint, whether it was an endpoint that was clearly better than all of the others.

The sponsor has identified any number of alternative ways of looking at rejection, and in particular, they had seven different yes or no criteria. My understanding is that all of these criteria have merit, even though they did identify one of them in their analysis as primary.

Well, in situations where you have as many as seven different dichotomous criteria, all of which have merit but none necessarily dominates the other as the clinically best in terms of universal consensus, one way to proceed is to create some overall score that combines the endpoints.

The principle is similar to the same way you combine centers in a multi-center study or the way in which you integrate studies in terms of an integrated analysis of efficacy. You put all of the information together.

Now in this particular case, we had seven endpoints. We could assign a score of one if you fail, zero if you succeed, and you can add them altogether to create a measure of total failure for patients. The higher the score, the more endpoints they failed. The lower the score, the more endpoints they were successful on.

Then you can essentially do a statistical

analysis. This is sometimes called an O'Brien score. It's based on the principle of looking at multiple endpoints. It's a concept that has been used in stroke. It's a concept that's been used in neuropathy, for diabetes. It's a standard statistical method for dealing with endpoints when you don't necessarily know where one is dominant over the others.

It's a method that, obviously, should have been preplanned in the protocol of this study when they knew that there was debate among the endpoints, and they knew they had difficulty choosing among them.

Nevertheless, if you proceed with this particular overall composite variable and you apply a Mantel-Haenszel trend test, which is a standard method, hopefully, you'll get the result on the next slide.

So this shows essentially the definition of a composite, and it produces an overall p value of .027. This means that, when you look at the separate endpoints, and some of them show significance and some of them show borderline nature and some of them are not significant at all, and you ask the overall question, how do we identify whether or not -- what's due to chance and what may be possibly real, one way

of proceeding is simply put everything together and see whether that tells you something.

In this particular case, it does yield a significant result, nevertheless, one post hoc defined, but certainly something that allows you to look at everything together.

The next display: In this particular case, six of the components are used, because there may be debate as to whether the seventh one should be in there, and the result is .034 when you do that.

This is something that you can take into consideration. It is, as we've expressed, post hoc. It is something that should have been part of the protocol, but it does say, when you put everything together, there is enough consistency among these endpoints to show an overall effect.

DR. HUNSICKER: I have a specific question about that statistical analysis in that these endpoints are, by their definition, highly correlated, and I'm very dubious that you can legitimately cumulate the outcomes when they are so highly correlated. You don't really have -- These layers are not independent of one another, as they might be if you had, for instance, neuropathy and retinopathy, which are maybe clinically correlated, but they are

definitionally separate.

This is a series of nested definitions, and I think probably that method is not legitimate.

DR. KOCH: Actually, this method is most appropriate when the endpoints are correlated and is a method that you would not use if they're independent. The fact that they are correlated means they go together.

Basically, because they're correlated, it means adding up a total score identifying the extent to which there's more failure events of the one kind than there are of the other kind is indeed a perfectly valid thing.

This method is actually identified as a method of choice when you expect the endpoints to be correlated. You would not use this method if you believe they were independent.

CHAIRMAN MASUR: We'll get back to this. Let's take two more questions. Then Dr. Goldberger has only allowed us six minutes for a break.

DR. GOLDBERGER: It is well known that the length of the break is solely at the Chair's discretion.

DR. WOODLE: Let's do away with the two questions.

CHAIRMAN MASUR: Steve?

DR. PIANTADOSI: I had a series of questions about methodology. I just wanted to be reassured that we were going to come back to that.

CHAIRMAN MASUR: Yes, we are definitely coming back to it.

I thought what we would do is we would let the FDA do their presentation, and then we will reopen the discussion on methodology. Then Wafaa, you are between us and the break.

DR. EL-SADR: And I'm not a cardiologist either.

CHAIRMAN MASUR: And the clock just started ticking. So go ahead.

DR. EL-SADR: And a good question. I'm assuming all along that, when you -- for your endpoints, this is the first episode of rejection. I mean, patients could have multiple episodes. I mean, it's reflecting again that I'm a neophyte as well.

DR. MAMELOK: Well, for each of the endpoints you meet the endpoint when you have the event the first time.

DR. EL-SADR: First time? Did you look at multiple episodes?

DR. MAMELOK: We have looked at multiple

episodes of rejection. Yes, could I have that slide, please?

This is the mean number of episodes of rejection during six months post transplant, and for biopsy proven rejection there were an average of 1.1 episodes in the AZA group, and 1.03 episodes in the MMF group, and similarly for biopsy or presumptive rejection there were 1.19 episodes in AZA and 1.07 in the MMF group.

DR. EL-SADR: Do you have it in the enrolled group?

DR. MAMELOK: Do we have that same slide in the enrolled group?

CHAIRMAN MASUR: Wafaa, does that answer your question? All right. We'll now take a four and a half minute break, and when we come back --

DR. STEMPIEN: Oh, excuse me, Dr. Masur. Since Dr. Miller will not be here when you reconvene, are there any final questions for Dr. Miller? I didn't know if the committee wanted him to respond to either of the questions or anything else.

CHAIRMAN MASUR: I think most of the remaining questions are methodologic.

DR. STEMPIEN: Thank you.

(Whereupon, the foregoing matter went off

the record at 10:52 a.m. and went back on the record at 11:04 a.m.)

CHAIRMAN MASUR: All right. If we could get the committee back and Dr. Korvick -- We have Dr. Korvick. So we now just need the committee.

All right. We're now going to proceed with the FDA presentation with Dr. Korvick and Dr. Elashoff, and then we will have a question period again, which I'm sure will focus on methodology.

Whether or not we will take a lunch break will be determined later. We will try to work through lunch and stop for dinner. Joyce?

DR. KORVICK: Okay. I'd like to have the first slide on. I guess we could have the lights down. Thank you.

I'm Dr. Korvick, primary medical reviewer for the NDA CellCept for cardiac transplantation.

This is a list of all of the primary reviewers who contributed the review. Today only myself and Dr. Elashoff, the statistician for the project team, will be presenting.

Next slide. This is an overall brief outline of what -- This is a brief outline of the FDA presentation. I will make some comments regarding the background and the study design. Dr. Elashoff will

make the FDA statistical presentation regarding efficacy analysis, and I will conclude with some brief comments regarding safety and introduce the questions for the committee.

It is our desire to focus on areas of the analysis where your comments will be helpful for us today in the interpretation of the results. Therefore, we will focus on primary outcome analysis and comment on safety data.

The application before you today is an extension of the renal indication which was approved in 1995. It's an extension as to cardiac transplantation. The applicant has presented background on the renal studies. However, there are several points we would like you to recall as you consider the cardiac transplant.

The renal indication was based on three well controlled, large studies demonstrating superiority at six months for the failure endpoint and equivalence at one year for the patient and graft survival.

Secondly, two doses of CellCept were studied in these trials. This was the three and the two-gram per day dose. The two-gram per day dose was recommended by the FDA in the label, and this was

based upon similarity of efficacy outcome and a somewhat higher amount of toxicity of premature withdrawal due to toxicity in the three-gram dose.

Finally, the cohort of patients in the renal studies has been followed for a minimum of three years for safety data as well as death and graft survival.

Given these points, the large database in renal transplantation, the double blind, well controlled study with extensive follow-up for safety, an agreement was reached with the applicant that one large, well controlled, double blind study would be sufficient for the extension of the indication to cardiac transplantation. The renal data would be considered as supportive evidence of efficacy.

Now I will turn my attention to the cardiac study. The applicant is to be congratulated for this groundbreaking study. Key elements of the design include: A large patient database with 650 patients randomized; the double blind nature of the study; the use of the azathioprine as a control arm; the extensive follow-up on all the patients that were enrolled; the angiography and IV ultrasound studies that were performed during the trial; and the use of routine endomyocardial biopsies at prespecified time

periods.

As the applicant has already described, the primary endpoint was changed in consultation several times with the FDA during the blinded portion of the study. The final agreement was for superiority for the six month death or biopsy proven rejection with hemodynamic endpoint and superiority at 12 months for the patient and graft survival -- excuse me, equivalence at 12 months for the patient and graft survival.

Both endpoints are of interest to the FDA. Several points were considered when this agreement was raised. It was recognized that azathioprine was not approved for this indication, and the majority of the useful historical data which was presented surrounded a one-year outcome for graft and death, and not the six month endpoint for rejection or hemodynamic compromise.

Consideration was given to several possible outcomes. One would be that, if CellCept were found to be superior at six months, this benefit should not be at the expense of safety at one year -- that is, a more profound immunosuppression resulting in excessive mortality and morbidity at one year.

Number two: If CellCept were found to be

equivalent at six months, the evaluation of the historical endpoint for azathioprine at one year would be explored. In this case, it would be necessary for the applicant to make the point that the control arm is efficacious.

I will now turn the podium over to Dr. Elashoff for statistical comment.

DR. ELASHOFF: I'll be discussing the efficacy of mycophenolate for this application.

The first issue I'll address is that of treated analysis compared to the intent to treat analysis. This issue applies both to the rejection endpoint and to the survival endpoint. I will then discuss each of the co-primary endpoints in turn.

Throughout this discussion, I will highlight the disparities between the protocol and some of the analyses presented by the applicant.

The protocol stated that all patients randomized in the study will be included in the inferential analyses on the basis of intent to treat. Additional analyses of efficacy variables may be performed using data from patients receiving at least one dose of study medication.

It is clear from this statement that the primary analysis would be the intent to treat analysis

with all patients, and the treated analysis would be viewed as secondary.

The applicant elected not to modify the primary intent to treat analysis after it was known that 11 percent of patients failed to receive study drug. However, in the NDA the background document and the presentation the applicant has emphasized the results of the treated analysis rather than the intent to treat analysis.

Since the change in focus occurred after the data were unblinded and analyzed, we are concerned that the treated group analysis was emphasized because of the more favorable results. This is not to say that the treated analysis is necessarily flawed.

If we grant that the decision to administer study drug was presumably made in a double blinded fashion, then the randomization was presumably not disturbed. In addition, the treated analysis is a clinically relevant analysis. However, the point is that performing several analyses gives multiple chances to win, and thus the p value for the analyses other than intent to treat should not be taken at face value.

The intent to treat analysis must still be viewed as primary, and p values in the treated

analysis should be adjusted to reflect the multiple comparisons. This adjustment means the p values in the treated analysis should be multiplied by a number a little less than 2.

For example, the p values in a treated subgroup of about .05 should be viewed like a p value resulting from a single analysis of about .08 to .10. This will apply both to the six month rejection analysis and to the 12 month survival analysis.

I will now turn to the first co-primary endpoint, biopsy proven rejection with hemodynamic compromise. This endpoint was evaluated at six months post transplant.

As Dr. Korvick mentioned, since azathioprine has not been demonstrated to be effective for rejection in this setting, it was felt necessary for the applicant to demonstrate superiority.

The six month rejection endpoint was composed of biopsy proven rejection accompanied by hemodynamic compromise. Death also counted as an event in this analysis.

This table shows the observed results. The results indicated no significant difference between the arms in either the intent to treat analysis or in the treated analysis. After the trial

was unblinded and these data were analyzed, the applicant, in conjunction with the steering committee, decided on a new endpoint.

One of the stated reasons for this change was that the event rate of rejection plus hemodynamic compromise were about 33 percent, which was felt to be too high compared to the 10-15 percent expected when the endpoint was chosen. This new endpoint was termed severe hemodynamic compromise. However, it was clearly known that the percentage of these events was higher than expected long before the study was completed.

So analogous to the intent to treat versus treated decision, the applicant chose not to change the definition of the primary endpoint in the protocol prior to unblinding, analyzing the data, and calculating the p value.

Since there was some confusion earlier at this point, I'll just repeat it. The percent response was known prior to the trial being unblinded. So there was the opportunity to change the endpoint prior to analyzing these results, calculating the p value. We must, therefore, view very skeptically the results for the new endpoint.

In addition, there was already a protocol

defined severe hemodynamic compromise definition that, while not specified as an endpoint, was used to manage patients. The protocol definition of severe hemodynamic compromise differs from the new derived severe hemodynamic compromise endpoint.

As this table shows, no significant difference was seen between the arms for the protocol specified severe hemodynamic compromise definition in either analysis. Recall, one of the main justifications for the new endpoint was that the more restrictive definition resulted in event rates closer to the expected 10-15 percent. However, as you can see, the rates for the protocol definition were also in the range of 10-15 percent, and this definition was felt to be clinically relevant since it was used to assist in the clinical management of patients.

The applicant also presented several other rejection analyses. Here I've summarized the rejection endpoints and their associated p values. Those in yellow were those in the protocol, and those in white are the ones that the applicant has presented that were not in the protocol.

The first line has the p values for the primary endpoint analysis. Since it was primary, these results must be given the highest weight in the

overall assessment of rejection.

The next lines have the new and the protocol severe hemodynamic compromise definitions. The following line is colored green to distinguish it as an FDA analysis. At Dr. Korvick's suggestion, I analyzed the event, biopsy proven rejection plus inotropic support, which was felt to be the most serious of the components of hemodynamic compromise. This endpoint showed no difference in either analysis.

Also listed are the secondary rejection endpoints from the protocol. None of these were significant in either the intent to treat or the treated analysis, even if one does not apply any multiple comparison adjustment, either for the fact that there were two sets of subjects or for the fact that multiple endpoints were analyzed.

The applicant discussed two other endpoints. The first is the endpoint, biopsy proven rejection of grade 3 or higher, which was not in the protocol; and the second is biopsy proven or presumed rejection with immunosuppressant treatment, which was in the protocol but under the heading of variables that would only be looked at descriptively.

Again, we must place these p values in the context of the entire analysis. Many of these

analyses are clinically relevant definitions of rejection, but since so many analyses were done, even a nonconservative, multiple comparison adjustment would raise even the smallest p value they report to well above .1.

Overall, none of the planned primary or secondary rejection analyses yielded a significant difference in either the intent to treat analysis or the treated analysis, even without multiple comparisons adjustments. None of the unplanned rejection endpoints are significant, if one takes the multiple comparisons into account.

The smallest p values were for unplanned endpoints in a secondary treated analysis. As a final point, since these endpoint definitions are closely related and statistically correlated, consistency of results in favor of one treatment or the other is to be expected.

Thus, the fact that mycophenolate showed a small numeric advantage for several similar rejection endpoints does not compensate for the fact that none of these endpoints demonstrated superiority on its own.

In summary, on the basis of this trial, the applicant did not meet the goal of demonstrating

superiority of mycophenolate over azathioprine with respect to six month rejection.

The two arms appeared to have similar efficacy for this endpoint. However, no information regarding the efficacy of azathioprine for any definition of six month rejection has been presented. Thus, the meaning of similar efficacy for this endpoint is unclear.

The other co-primary endpoint was 12 month survival. The applicant proposed to demonstrate equivalence for this endpoint. Equivalence would be based on the lower bound of a 95 percent confidence interval, on the difference in survival rates between mycophenolate and azathioprine.

The applicant proposed that equivalence be defined as lower bound of this confidence interval being greater than -10 percent.

I will illustrate the equivalence calculation with a small example. For example, if there was a 90 percent survival on the experimental arm and 87 percent on the standard arm, the difference would be three percent.

This difference has an associated variability. So we construct a 95 percent confidence interval around this difference of three percent. In

this example, we calculate a confidence interval of -2 percent to +8 percent.

Equivalence is primarily based on the lower number, in this case -2 percent. In this example, we would compare -2 percent to -10 percent and find that equivalence has been demonstrated for this example.

I will now turn to the actual results seen. In the intent to treat analysis, the observed difference was 2.6 percent with a lower confidence bound of -2.5 percent. On the basis of this result, we believe that equivalence has been demonstrated. However, the applicant has emphasized the result in the treated subgroup over the intent to treat analysis.

Recall that the applicant elected to keep the primary analysis as intent to treat prior to unblinding. The change in emphasis occurred after the more favorable result in the treated analysis was known. However, even with this change in emphasis to the treated subgroup, the conclusion is unchanged.

The treated results fell within the protocol definition of equivalence. The protocol stated that the mycophenolate arm would have to be ten percent better to conclude superiority, and the

treated analysis did not come close to meeting this goal.

An equivalence design allows efficacy to be demonstrated even when the experimental arm is somewhat worse than the control. Conversely, though, if the experimental arm is a little better than the control, the claim of superiority should not follow automatically.

The applicant has focused on the fact that the lower confidence bound in the treated analysis was greater than aero percent with a p value of less than .05. However, several points can be made regarding this claim.

First, the primary hypothesis was equivalence and not superiority. As I mentioned previously, this means we would need to see compelling results for a claim of superiority. However, for several methods of analysis, had there been one less death in the azathioprine arm or one more in the mycophenolate arm, the lower confidence bound would have been less than zero percent with a corresponding p value above .05.

Additionally, there is the concern over the p values from the treated analysis that I discussed earlier, namely, that the treated results

may have been emphasized due to the more favorable results.

The protocol specified intent to treat results clearly showed equivalence and not superiority. Observed p values in the treated group of about .04 to .05 are more like p values of .08 to .10. Thus, these considerations lead us to conclude that the treated results, while suggestive, does not demonstrate the superiority of mycophenolate for one-year survival.

To summarize the survival results, we feel that the applicant has demonstrated equivalence. However, we feel that superiority has not been established. There is a suggestion from the observed survival difference that mycophenolate might provide some advantage, and this can be revisited when longer term follow-up has been completed.

To put these results into perspective, I will briefly summarize the data presented on azathioprine.

The data supporting the effect of azathioprine on 12 month survival come from several epidemiologic studies. The two large studies the applicant has presented are the Opeltz and the Shumway studies. Both indicated a survival advantage at one

year of about 4 percent.

In interpreting these findings, one must keep in mind that the results are confounded by time. This confounding results from the fact that the studies looked at heart transplants occurring over a multi-year period.

During this time period, the frequency of triple therapy may have increased, while at the same time survival may have improved for reasons not related to triple therapy.

Studies such as these cannot separate these two contributions to the increased survival. Thus, the value of 4 percent may, in fact, be an upper bound on the survival advantage of azathioprine.

Both studies also indicated that the benefit of azathioprine may be limited to the first year of treatment with no additional benefit accruing after the first year.

Finally, no data were presented for the effect on azathioprine on any definition of six month rejection.

In conclusion, the applicant met one of the two goals of the study. The applicant has demonstrated equivalence for the 12 month survival endpoint. There is a suggestion from the observed

survival difference that mycophenolate might provide some advantage, but this result does not meet the burden of proof for a claim of superiority.

The applicant failed to demonstrate superiority for six month rejection. It appeared that the two arms did have similar response rates for this endpoint. However, the import of this finding is uncertain, since AZA has not been shown to be effective for six month rejection.

I will now turn back to Dr. Korvick.

DR. KORVICK: I will now comment on the safety of CellCept. I think, in general, we're in agreement with the presentation that you heard earlier by the company. In addition, I think it's important to remember that, when one looks at the overall adverse event rate, these patients may tend to be a little bit more ill than patients receiving transplants for renal -- renal transplant.

In addition, these patients are being treated with multiple other concomitant medication, which may add to the toxicity.

In general, we believe that the overall adverse event profile is similar to that of the renal transplant population for the one year data. This slide again is just a comparison of the one year

safety data in cardiac transplant and renal transplant for some major events. Of interest, death, malignancies, OI, serious adverse events and premature withdrawal due to adverse events.

I think it's instructive to look at the 3 gram cardiac and the 3 gram renal events. Overall, they're relatively similar. Some differences do stand out which was pointed out earlier by the applicant, for opportunistic infections at 3 grams and the 3 gram in renal is a little bit higher. These were mostly due to some Herpes infections and, of interest, these patients weren't dying more frequently due to those infections.

In addition, they had some serious adverse events, about 10 percent for cardiac and about 8 percent for MMF. The differences in these were mostly due to leucopenia, and again these patients were not dying directly of their leucopenia. However, that may have been reflected in some of the deaths due to infection.

Another point we would like to make is that it would be of interest to follow these patients further, as the company will be doing, for safety at three years. When we did have this data for renal at three years, the incidence rates for these various

events were not that much different, and only slight increases occurred across arms.

Again, the 2 gram dose is approved for renal, not the 3, and at the three year endpoint for renal, these differences between the 2 and 3 gram dose were not that strikingly different.

So in summary, our conclusions would be that CellCept appears to be similar to azathioprine for the prevention of biopsy proven rejection or six month -- or death at six months, and that CellCept is at least as good as azathioprine for prevention of death or retransplantation at one year, and that the safety profile is similar to that seen in renal studies specifically comparable to the 3 gram dose.

Finally, I would like to introduce the questions for your consideration later this morning.

Number one: Is CellCept safe and effective for the prevention of organ rejection in cardiac allograft recipients?

We look forward to your comments on future study designs regarding the six month endpoint, the design of that and the choice of control arm therapy.

Thank you.

For your convenience also, I neglected to mention that our slides are in your blue folder. That

concludes our presentation.

CHAIRMAN MASUR: Are there questions for Joyce? Larry?

DR. HUNSICKER: Hunsicker. The evolution of the discussion has focused a lot of attention on the question of equivalence, and I'd like to spend a little time discussing the issue of the effects of azathioprine, both on survival at a year and on graft rejection.

I have a specific question which you may be able to answer. In the two analyses that were registry analyses that -- I can't remember the name. I never remember names, but our statistician from the FDA presented -- Michael -- which are the two that I would have chosen for trying to peg something, because they're both very large registry analyses.

It would be customary -- I know that we do this at UNOS all the time -- to correct for year of transplantation as a way of eliminating the time bias. Was that correction made in those two studies?

DR. KORVICK: I don't believe that it was, but I'm not as familiar as the people who have -- I've only read the articles, but I don't know if someone --

DR. HUNSICKER: You might ask of the people -- If we have the papers, it would take two

seconds to find out, and I know that several of the references the folks from Roche may have available.

This is a fairly critical issue, because I think that one could estimate that the benefit at one year is of the order of four percent if, in fact, there is a correction for year; but if there is not, the presumption would be very strong that the dual therapy would have been in earlier years. That was when they were being done, and triple therapy would have been later and, as has already been said, there are just dozens of reasons why the outcomes could have improved four percent in that period of time.

So if those are corrected, it will make a substantial difference to my interpretation of that outcome, and I would invite them to see if they can find those references.

The stuff that we were given, I think, answers the second question. We have sort of retreated somewhat to the assertion that mycophenolate is equivalent to azathioprine for prevention of rejection in cardiac transplantation. Unfortunately, this raises the traditional question: If it is equivalent, it isn't clear whether it's equivalent in efficacy or equivalent in efficacy.

There would be the presumption that

something that was preventing rejection in one circumstance would prevent it in another, but we actually have, as I understand, virtually no information about the impact of azathioprine on the rate of rejection within the first six months in patients treated also with cyclosporine and prednisone, but I would like to be educated, if there people who do know of more information.

CHAIRMAN MASUR: You might also -- Dr. Elashoff, I just point out that some of these papers are in Appendix 8 of the book.

DR. KORVICK: I think it's in the background.

CHAIRMAN MASUR: Joyce, maybe you could respond to that. Maybe one of the sponsors would like to respond to whether or not azathioprine is effective or ineffective.

DR. KORVICK: I think the reason that we chose to focus our analysis with regard to azathioprine on the one year equivalence -- we felt comfortable with that, because there were data that were demonstrating that effect which, as was pointed out earlier -- it's easier to look at, dead or alive. That's a pretty straightforward endpoint.

We believe that how one would have

measured rejection at six months, the methodology for that, would have been changing over time, and that it made it more difficult for us to understand what the endpoint would have meant at six months in comparison to the historic control data.

As you know, the international criteria for biopsy classification is relatively new. So we are less sure of what that would mean if it was not superior at six months. Mike want to comment as to the other. I would defer to people who are expert in the field.

DR. ELASHOFF: Yes. Just that I think that's why -- in contrast to the equivalent comparison.

DR. HUNSICKER: I've actually looked at what was in Appendix -- whatever the number is here -- 8, and they have provided the figures but not the text; but I actually can make an educated guess, because what they're presenting here are Kaplan-Maiers, and you can't correct for time on a Kaplan-Meier.

So I assume that we are looking at uncorrected survivals. If they are uncorrected for time, then the upper estimate of four percent benefit from use of azathioprine for the one year end point

would suggest that that is indeed an upper estimate of the likely effect, because it's likely partially due to time.

The other thing I would put in is that the experience from other circumstances is relevant here. There was a small numeric but nonsignificant advantage to the use of mycophenolate in the kidney trial. It was a rather small advantage which was confined to the first few months after the transplant where there were excess graft failures.

That's the comparable thing, but it was not statistically significant at any point, and I think we can say that there isn't a reason by way of prior probability for assuming that there would be a substantial impact of azathioprine -- I'm sorry, this is a sort of a four-way around comparison.

DR. KORVICK: I think we're going back to the renal transplant, though. Regarding comparisons for efficacy, it was difficult because of sample size. I think, when you try to tease out whether the 2 gram or the 3 gram was better, those were limited; but if you took the 2 and 3 gram as an aggregate --

DR. HUNSICKER: I should have clarified. I'm doing a semi-legitimate comparison which actually has been made by the company, and that is, if -- with

the same caveats. It's only semi-legitimate.

If you match up the three trials, two of the trials were mycophenolate versus azathioprine, and one was mycophenolate versus placebo.

DR. KORVICK: Right.

DR. HUNSICKER: In fact, the mycophenolate rates were very similar, and you can then sort of compare what was the impact of azathioprine. This suggests, similarly, about a five percent prediction against rejection rate, and no impact on survival at the end of the first year.

This is an indirect comparison. I want to make it very clear, but the assertion of an impact on survival of the graft, which is at most four percent and possibly less than that, is consistent with what was seen in the renal trials.

DR. ABERNETHY: I guess I'd like to ask the transplant clinicians -- I mean, I'm assuming that the reason azathioprine was included was that there was an assumption that the study would not be recruited because the standard of practice was inclusion of azathioprine.

So if that's correct, then it seems like what we're kind of trying to work around is not having to ask the sponsor to prove whether azathioprine is

effective, which seems a fairly reasonable thing not to ask them to do, and at the same time to think about what the control group is.

I guess that I'm trying to sort us through. I guess that's why the FDA then requested superiority. However, they're asking a request for superiority over a standard of practice, and so I'm just trying to sort that all through in my mind. I guess I'd like for some of the transplant clinicians to help me a little bit with that.

DR. PINA: I can't speak for the steering committee, and maybe Jon can probably do that, but I know that there would have been tremendous amounts of resistance, at least in this country, to do the trial without the control group having azathioprine, simply because that's what we do.

There was probably a reference -- I wasn't at that meeting -- made to the transplant research database, which is an inclusion of cardiac transplant centers, most transplant centers around the country, and it's a very robust database, using primarily triple therapy.

I don't know of any analysis unless you do, Jon, that Alabama has made of dropping azathioprine and doing cyclosporine and steroids

alone. I don't know of any such analysis. So I think there would have been tremendous problem in recruitment, had that not been the case.

DR. KOBASHIGAWA: Jon Kobashigawa.

When the steering committee -- Actually, when the total group met prior to the study itself, there was overwhelming support for the use of triple drug therapy. That was mainly because of the experience that all of us had had during the 1980s where survival rates improved dramatically.

There is no evidence in terms of rejection, and I agree, when you look at rejection, how do you gauge rejection when we can't even gauge it right now in terms of comparisons from era to era.

From anecdotal studies, Maria Theresa Oliveri was one of the first to publish that triple drug therapy did have advantages over conventional or dual therapy with cyclosporine and corticosteroids alone.

So it was standard of therapy at the time, and I think that's what should be reinforced here.

DR. PINA: And I think part of the issue, too, is our continuing concern about high dose steroids in this population, and many centers are now trying to remove steroids at a year. I know we're

trying to remove them at a year, simply because of the long term side effects.

As these people live longer and longer we're starting to see the ravages of steroids. The second reason is to try to decrease the cyclosporine negative effect on renal function where earlier on, when higher doses were used, a lot of patients ended up having to have kidney transplants after so many years, after their heart transplant.

I have a question concerning cyclosporine. Do we have any data on any interaction between cyclosporine levels and the rate of rejection, comparison between the azathioprine group and the MMF group?

DR. MAMELOK: We don't have any specific data that explicitly defines relationship of cyclosporine levels to rejection. The cyclosporine levels between the two groups, both in the enrolled and treated population, were the same. It was monitored throughout the trial. So they were comparable, but we didn't look at what the effect of those levels were.

DR. PINA: And the reason I asked that is, to make it even more complex, there's arguments about where the cyclosporine level should be a year later,

two years later, and centers have argued, and we've done other studies where people have had to get together in a room and say, okay, what will be an acceptable cyclosporine level after a year, after two years.

So there's even arguments about that.

DR. MAMELOK: Yes, and Dr. Kobashigawa wanted to add one more point related to the efficacy of azathioprine.

DR. KOBASHIGAWA: When we went to triple drug therapy in the mid-1980s, I wanted to reinforce that there was another reason for doing so. That was to decrease doses of cyclosporine and corticosteroids which, notoriously, were much higher prior to the start of triple drug therapy.

So, basically, there was somewhat of a benefit by adding azathioprine and decreasing the side effects of these other two drugs.

CHAIRMAN MASUR: Larry?

DR. HUNSICKER: I don't want to disagree in any way with the choice of a triple drug regimen. I think it would have been -- Just to be absolutely clear for everybody's sake here, it would have been impossible to conduct this trial with a cyclosporine/prednisone comparator arm. You couldn't

have recruited patients.

We've learned a whole lot about the value of azathioprine in renal transplantation in the last little while, and that may reflect on what might be done in the future; but this study was started at a time that, even in kidney transplantation, the use of azathioprine was virtually universal, but the issue does arise when you have proved equivalence to something whose value is not known what you have proved.

I have no more interest than you do in trying to turn this into a review of the efficacy of azathioprine, but if you proved equivalence to a drug whose value is not known, you don't know whether they are equally useful or equally unuseful, and that becomes an issue.

Now the relevance of that is to the definitions of the goals of the study. This study was designed in a way very similarly to the kidney studies. It was designed -- and I read here now from the FDA's notes, not what the sponsor has given. The compromise agreed upon -- I think we need some comment on this -- was superiority at six months on acute rejection with hemodynamic compromise while simultaneously demonstrating equivalence for one-year

patient and graft survival.

Now as I sat through the renal thing, the issue then was whether it was a reasonable goal to approve an agent that simply reduced rejection rate, and the decision was, yes, that is a legitimate goal. The inclusion of the survival thing there was to make certain that we didn't reduce rejections while killing people in the meantime.

That is to say, the survival outcome was let's at least make sure we're not killing people. If you read that here, the primary goal, if you will, was to show -- and I think it's a reasonable extrapolation -- was to show superiority of mycophenolate over azathioprine, exactly what was, in fact, shown in the kidney trial and which, I think, we have not really shown here, with the survival issue being there as a safety caution, that we weren't knocking people off in the course of preserving their grafts.

When the goal of superiority in what is in some fashion, you know, the more equal of the two equal goals, sort of slips into equivalence, then I really sort of find myself nowhere in trying to figure out what I'm proving in terms of efficacy.

DR. GOLDBERGER: Henry, let me just make a couple of comments. I think Dr. Hunsicker certainly

described what the original intents of the study were as described in the background document, and I think as described by the company as well.

The original intent was for superiority at six months. Obviously, when you are dealing with the issue of an unapproved comparator, it is much simpler to utilize that approach, with the idea that the 12 month endpoint would primarily be for safety, for the reasons that have been outlined, i.e., getting some benefit at six months versus the issue of having increased mortality at 12 because of excess immunosuppression.

I think that, as far as then looking at what actually happened in the study, there's obviously a couple of points to make. One is that it's, you know, incumbent upon us to get the best possible advice when things do not work out entirely as expected.

I think, given that first we have a result of equivalence at six months to the endpoint using azathioprine, which has been acknowledged by virtually everyone is the standard of care and would not be possible to do the study without including it, we're then faced with a situation of we're not sure what azathioprine is doing, but everybody is using it. So

we have to deal with that issue, from which we, therefore, need expert advice from those people who are, in fact, actually using it.

As to the 12 month endpoint, its original goal, as it was in the renal study, was as a safety endpoint vis a vis the issue of excess immunosuppression. Nonetheless, it is hard not to also consider what a result at 12 months means in terms of a question of a possible mortality difference or mortality benefit in favor of MMF.

Then again, what we are supposed to do with that -- I think it's probably not prudent to at least not consider that a little bit as possibly an efficacy benefit as well. We then again need advice first from the analytic side as to what to make of this, given the caveats that have been described about the multiple comparisons, etcetera, plus from a clinical perspective, looking at the magnitude of the effect, what the clinicians think about this.

An issue that I'd like to raise to help us in our own internal thinking is the following. When I look at some of the data from the overall group, the all randomized, as well as, to some degree, the treated as well, one of the things that does strike me is that a fairly substantial portion of the overall

number of deaths that occur in the first year seem to occur quite early, in some cases probably within the first few days to first week or two.

The question comes up, how much benefit can you reasonably expect from azathioprine versus MMF in that patient population? If, in fact, a lot of those patients might not be candidates to be able to be helped, what does that say about the ability to show a mortality difference at a year, and how should we interpret marginal mortality differences at a year, in light of that?

That's the kind of thing we could again use advice from committee members who are more familiar with these issues.

DR. STARLING: If I can make a few comments. The last comment that you just made, Dr. Goldberger -- I asked a question earlier this morning that was addressing that issue, and the way I asked it was to -- I wanted to know about the PRAs.

I wanted to know about data on perspective cross-matches and wanted more information, really, related to the use of induction therapy, plasmapheresis, what most of us in the cardiac transplant community would identify as high risk patients.

I think your point is well taken, that if you include patients like that at the front end that come into the procedure very, very high risk, yes, it would be important to know what the impact is of MMF on that patient group; but I think that's a separate patient population to look at.

The second comment that I wanted to make is a more global one. That is, to put my comments in context, I've worked around cardiac transplantation since 1981, initially at the University of Pittsburgh, and have kind of lived through cyclosporine, Fk506, etcetera, etcetera.

I really think the most compelling information that I've seen presented today -- and I did not participate in this study; so I'm naive to this study per se -- is mortality information.

This study says to me, now speaking as a clinician and not as an analytical biostatistician -- It says to me, one, we don't know how to diagnose rejection. Okay? But the key endpoints in our patient population are death and retransplantation.

I think we should pay very close attention to that fact.

CHAIRMAN MASUR: Any other panel members want to respond to Dr. Goldberger?

DR. PINA: Again from the clinician's standpoint, and I agree with Randy that many of the questions that he asked would have identified the very high risk. One of the highest risk patients that we see are the patients who are so ill prior to undergoing transplant that I wonder if they would have even been considered, because they were too ill, intubated, etcetera, sedated, to actually sign an informed consent. These may be the patients that you can't give anything oral to for several days, because they are still intubated, if they survive.

So I think, yes, I would like to know as a clinician what are the benefits of any drug that I could give early and impact early on long term survival, because we know even without looking at these data that the sickest patients that keep rejecting early are just simply not going to do well by the end of -- It doesn't even take a year. It takes six months.

So I think that's critical information. I am actually kind of surprised as a clinician -- and we've been talking about this, Randy and I -- to see the number of 3A rejections, you know, within the initial follow-up period. That seems to me to be a bit high compared to what I see anecdotally, you know,

on a day in, day out basis.

We both now come from probably one of the largest, and Jon -- Probably, the three largest programs are represented here.

CHAIRMAN MASUR: You're surprised. What would you attribute the high rate of rejection in this study to?

DR. PINA: I don't know. I don't know the reason, but I think that the number of 3A rejections looks to me higher than what I've seen, and perhaps Jon can comment from our transplant research database. Seems to me a bit high.

The number of 1As, no. I mean, 1As are extremely common. I tell patients you will probably reject at least once during this year, period.

CHAIRMAN MASUR: Well, almost everybody in this trial had a 1A. Right? Ninety-seven percent?

DR. PINA: That doesn't surprise me. It's the 3As that I'm commenting on.

CHAIRMAN MASUR: And it's not an issue of pathologists outside of the study using somewhat different criteria, not being as standardized. They're all pretty well standardized?

DR. HUNSICKER: Maybe I could make some comments. Do you want to comment on that issue, Jon?

Go ahead.

DR. KOBASHIGAWA: Yes. Thank you. The cardiac transplant research database published data on 3A rejection several years ago, and 40 percent at one year were found to be rejection free -- of 3A rejections. So 60 percent actually had 3A rejection, albeit that was about four years ago.

We are improving. So that probably comes down to about 50 percent at this point, and that's basically what -- right, pretty much shows. I think we're rather in line with the incidence of 3A rejection.

Granted, there are many issues on what else constitutes rejection.

CHAIRMAN MASUR: Larry?

DR. HUNSICKER: The FDA asked two questions. He has now disappeared behind somebody's head there. One was how to deal with the issue of mortality and the numeric superiority of mycophenolate with respect to mortality when the original stipulation was equivalence, and then the importance of early events.

These are basically statistical and biological in nature, respectively. So let me talk about the biology first.

The early mortality following cardiac transplantation within, let's say, the first week is mostly independent of chronic immunosuppression. This is related to cardiovascular surgical problems and probably will not be affected by any of the agents that we currently give.

A small fraction of patients have preformed antibodies which are, in fact, rejection related, but it is not documented that any of our approaches of drug therapy at least, leaving out the issue of plasmapheresis, deal effectively with the impact of preformed antibody.

So it is unlikely that deaths within the first week, let's just say, have anything to do with the drugs. From a point of view of trial design, you know who's in trouble pretty much right after they come out of surgery. It's pretty obvious who's in trouble, and these are the people who stay intubated for five days and are struggling along, and they are really not the group of people who you would want to look at.

So for future trials, I would be very happy to -- not randomize -- to enter patients into the study before they go to surgery so that you can get consent and all of that, but not randomize them

until you know that they are out of this really high risk period, because these are not the patients that are relevant.

I actually agree with the sponsor that, if it had been prospectively defined, the treated group which should have been randomized right at the time the treatment was started would have been the appropriate group to look at, because the early deaths are really unrelated to the drug treatment. However, we didn't get that way, and then we have the problem that -- Michael, is it? -- raised, which is it's not really fair to get two cracks at that success, and that's a problem that I have.

So I would suggest to you that the early deaths really are unrelated to drug treatment when you're speaking within the first week. Beyond that, maybe it's different, and I think we should get some consultation from the cardiologists as well.

Would you agree that that's a reasonable separation point?

DR. STARLING: Well, not to confuse the issue, but I think, clearly we see patients that do not have elevated PRAs at the time of transplant that come into the procedure as a -- and this is a small percentage of patients -- come into the procedure as

a low risk patient, and then through techniques such as flow cytometry are able to delineate a day four/day five, a big shift in a lot of antibody to donor specific antigens. Those are very difficult patients to get through the procedure.

DR. HUNSICKER: I'm not asserting that the early deaths are all nonimmunologic. I'm just saying I doubt that our acute immunosuppression has got anything to do with them, other than for plasmapheresis and related things, which may or may not.

DR. GRIFFITH: I can make a comment, not as a cardiologist but as a cardiac surgeon. That is that you have focused on, you know, probably an irrelevance relative to the combination of drugs.

You know, we spent a long time trying to tell people not to give cyclosporine preoperatively in cardiac pulmonary bypass patients, and people kept saying you had to give it, you know, before the patient saw the graft.

Well, you know, the final analysis is, in fact, you can give cyclosporine anytime in the first few days after transplantation without any ill effects on terms of outcome, and far better renal function. So that, you know, people have prejudices in all

manners of ways, but the bottom line is these patients that didn't do well early probably wouldn't have done well early, regardless of the regimen. I agree with that.

In fact, the survival differences I understood the Kaplan-Meier curve -- and this is directed to you, Mark -- with respect to the treated patients -- and I've forgotten, really, what it looked like in the enrolled or intent to treat trial; but at least in the treated patients, the separation which appeared to occur did so after six months.

You know, it's almost a shame we can't see this as a three-year trial, because if that were to continue at the same slopes, you would see a far different significance. My opinion would be, if the trial were larger, as it might have been in a renal based trial, the separation we're seeing at 12 months in survival, which may not meet your strict criteria in terms of statistical analysis, in my mind is meaningful.

If you look at -- not a five percent difference. If you look at a 45 percent reduction in rate of death, that's the way a cardiologist, by the way, usually presents his data is, you know, not an overall actuarial difference but a percent reduction,

and that's a 45 percent difference in terms of those that were taking MMF.

In terms of numbers, there are almost twice as many people who died who took azathioprine as those who took MMF, and it's very hard for me as a clinician to deny that that is not somewhat different.

DR. MAMELOK: Dr. Griffith, we do have some survival data presented in the Kaplan-Meier curve for patients with nine months -- with experience on all -- well, not -- with nine months more follow-up. To be fair, it's not data that -- It was provided as part of the NDA safety update, and it's not data that the FDA has had a chance to review to try and replicate the analysis; but if you're interested in that, I could show it. If not --

DR. GRIFFITH: Well, I'm interested. Whether it would be considered relevant or not is another question, but I was just picking up on your point that you would like to see longer term follow-up.

DR. MAMELOK: Yeah. I mean, great.

DR. GRIFFITH: We should see all the data you have.

DR. HUNSICKER: While you're doing that, I think that it is the case that, as I had understood

what was said, it is still open that, if a substantial difference in late survival becomes apparent, this issue could be opened later again.

I say that, because one of the -- as all of the transplant people know, one of the early hopes of mycophenolate is that it would prevent graft arterial disease, which is the cause of death mostly in late cardiac transplants and the cause of graft loss in kidney transplant.

So it is entirely possible that at one year we would find nothing of any interest whatsoever, but at three or four years we might find something quite compelling.

DR. GRIFFITH: Let me just ask -- I'm sorry -- one question, because I didn't quite understand all that you were able to tell us.

In the sponsor's presentation relative to survival in the treated groups, they showed a p value of .03 difference at 12 months of a rate of survival. Do you argue that that's significant?

DR. ELASHOFF: Yes. I would say that it's not significant -- I would say that the p value -- I guess it was about .035, something like that. Since it's only being emphasized because of the more favorable results, I would say that it's not

significant. That's one reason, since when you do two analyses, there's two chances to get below .05.

The second is that in an equivalence trial you are in the setting where, if you're slightly worse, that's still okay. If you're slightly better, that shouldn't mean superiority. It should still mean a similar thing to slightly worse.

I think the point that several people are making that the early deaths are not really related to the study drug, and so one might not want to, you know, spend -- One might not want to analyze those.

If one was doing an equivalence trial and one was concerned that the treatment might actually be worse, it's an advantage to include those that don't -- that aren't related to the study drug. So I think that distinction has to be made.

Since the study was designed for equivalence, those early deaths unrelated to study drug may have furthered the goal of demonstrating equivalence.

DR. GRIFFITH: I guess I just don't -- I don't understand it, because I'm not sophisticated enough, don't have your background to understand why a p value separating two Kaplan-Meier curves of .03 is considered not significant, just because the trial was

designed to show equivalence. It's either different or it isn't different. To me, it's different.

DR. ELASHOFF: Well, no, that's not -- If you do several different -- For example, in rejection when you do, say, 20 analyses, you expect to see several with p value less than .05 by chance alone. So having a p value less than .05 no longer means what it means when you have one analysis and you're going to only do one comparison and get one p value and make one conclusion.

If you're allowed to do multiple analyses, pick the best one and draw a conclusion, p less than .05 doesn't have the meaning anymore.

CHAIRMAN MASUR: A very traditional approach is, if you had pre-specified two analyses that you would be required to be at, for example, the .025 level to say that sort of your overall chance of making a mistake and, in fact, there's no difference. It is still about five percent.

So if you just look at an unadjusted p value, it gives you the wrong interpretation. You have to try to take that into account. So what Mike was trying to do was give a suggestion that this is a .04, .03 is sort of like .06, .08 if you hadn't done anything else to try to put it into perspective, that

it wouldn't meet our traditional .05 level, but it's still reasonably unlikely to occur by chance, but it's not quite at that level we've all grown sort of comfortable with.

Does that answer your question?

DR. GRIFFITH: So -- Well, it does, kind of, although I might argue with you.

DR. PIANTADOSI: Could I just add one point here before you move on to something else.

The whole discussion presupposes the notion that p values are the right currency for interpreting these effects, and I would challenge that. I think that this discussion is an example of the fact that p values are not up to the task, particularly in equivalence designs.

Although we're mixing here some very important but different issues, one of which is how we interpret these particular data and another is how we design future trials, I would encourage the FDA not to insist on p value based definitions exclusively in designing future studies. However, I think there would be little argument in the presence circumstance that, because of p values being chosen as the medium for interpretation here, we do need to somehow compensate for the undesirable properties of p values,

and I think the FDA has done a reasonable job of that.

I did want to comment briefly, though, about the other issue that's flying around or one of the other issues. That is these early versus late mortality differences, because there are methodologic concerns there as well.

There certainly would be no argument if studies were designed routinely conditional on patients having passed that high early mortality point, and therefore, the treatment inferences would be based on what happens to them after that. I don't think there's any great mystery of how to do that or the desirability of it.

Strictly speaking, of course, it's not absolutely necessary, and one could extract the relevant treatment comparisons even in the presence of a fairly high early mortality, simply by making the study large enough and defining the endpoints appropriately.

So as a device for efficiency, it seems to me like it's a desirable thing to do, again, in the future, but doesn't really help us understand and interpret the existing data.

Now the argument has been floated around all morning that somehow we should be paying quite a

lot of attention to these analyses that condition on the patient's actually receiving the drug. In fact, we see that the results, depending on how you interpret them and whether you buy into the whole p value thing or not, depends in part on whether we take the treated patients or all patients randomized.

I saw evidence in some of the data that was presented that suggested a differential effect on the two treatment groups as a result of that subsetting. In particular, the Kaplan-Meier curves that we saw for the patients that were not treated were strongly different and suggested to me that patients with worse prognosis from the treatment group were being excluded.

Patients with not quite so bad prognosis from the azathioprine group were being excluded, and that differential, therefore, showed up in the Kaplan-Meier curves, which were quite different, and therefore, increased the difference between the treatment groups in the balance of patients that were included in the trial.

Now there's really only a couple of ways that that kind of effect could happen. Of course, one of them is by chance, and the argument of the sponsor is that these effects occurred by chance and,

therefore, the subset that we're left with is an appropriate comparison.

If you believe that, then you also have to believe that the differences that we're left over with are also caused by chance. So you can't have it both ways. You can't say that the subset is equivalent by chance, and the other group is differing not by chance, differing by treatment.

So I think we have to really be consistent about how we interpret those data.

The other explanation and the one that I wanted to ask about earlier was that the differences are not due to chance and that, in fact, there is some corruption in the infrastructure of how the trial was managed.

Obviously, the larger the differential between these two groups that are supposed to be randomized and masked, the more suspicious you become that there might be some degeneration of the infrastructure in the trial.

So I wanted to ask FDA to what extent they had reassured themselves that the randomization procedures, the administration and so on for this study would have prevented any discovery of treatment assignments and differential exclusions from the

treatment groups based on such discovery.

DR. KORVICK; I think, in general, from a clinical point of view, and then Mike wanted to make a comment, we have traditionally in cases like this sent out our field investigators, and they were sent out to two of the largest centers in the United States to look to see if there were any issues that we could uncover.

Specifically, we asked the question if they could uncover any problems in finding out about the blinding, and they were not able to find any.

On the second way, when you look at the way the study was designed and how the sponsor describes the capsules and the dosing, etcetera, will be blinded, at least from this end it seems to be done in a very good manner.

Perhaps some people who participated in the study such as Dr. Pina might want to comment about, you know, whether or not they could tell, but then you get into a kind of a funny debate about I knew the patient was on this and I knew the patient was on that, and it never seems to be borne out when we get into these discussions.

Dr. Elashoff also did some analysis.

DR. ELASHOFF: Yes, just to address two

points, one for the p values and the survival analysis. We agree that the p values are not the preferred method of assessing the effect of survival. That's why it was designed -- I mean, it was an equivalence design based on the confidence interval.

It was -- My comments were in response to the applicant's presented p values. As far as the issue of a possible chance imbalance, I think that's still a very important issue, and it's hard to know whether, in fact, the observed result in the treated subset was, in fact, capitalizing on a chance imbalance between sicker and less sick patients.

The number of deaths is relatively small, and so it's hard to pick out any one variable that might have accounted for that. I did some exploratory analyses, but the concept is very difficult. What is a sick person versus one who is not?

Any single baseline variable, even if it's imbalanced, may not adequately carry all the information exactly.

DR. PIANTADOSI: Well, that gets to my last question, which -- I think most of the methodologic concerns that I had were dealt with more than adequately in your presentation, but we saw no analyses that attempted to -- Well, let me back up.

Once you remove patients from the analysis, now you potentially introduce selection effects that might drive a treatment difference where, in fact, none existed before. One way to shed some light on whether that's going on is to do analyses that adjust for differences in the baseline prognostic factor composition of the two treatment groups. Yet we saw none of that. Was any of that done and, if so, what does it show?

DR. ELASHOFF: Yes. I did a lot of those kind of analyses, but the problem is in the treated group the number of deaths is quite small in both arms, and there is no one variable that sort of indicates this variable should be adjusted for, and then that would explain the observed effect.

So I tried all those variables, all the baseline variables that were measured. It could be some combination of variables might explain it or it could be just the sample size is so small that, you know, those analyses aren't going to definitively answer your question.

DR. SELF: We started this with a description of a subset of patients who did poorly -- so poorly so early that the issue of what immunosuppressive drug to use was irrelevant, but I

think we should distinguish that subset which, in my opinion, is legitimate to set aside, given assurances of the maintenance of the blinding and all, from the set of patients that were set aside in the treated analyses.

In fact, most of the patients who were set aside in the treated analyses received some immunosuppressive drugs. Most received AZA, and apparently, a few received the study drug as well.

So I wonder if there were any analyses that looked at setting aside only those patients for which the issue of drug choice is irrelevant, but retaining those for which it was relevant.

DR. ELASHOFF: Well, the issue of who was eligible to receive study drug seemed to be a sort of complicated one. In fact, in the dataset that I have there were people in the analysis who received study drug, say, day six, seven, I think on up to ten.

So the question is: By the protocol definition, those people shouldn't be in the analysis, but they did receive at least one dose of study medication. I mean, it's -- Once you start picking out who to exclude and who to include, there's lots of, you know, possibly interesting ways of doing that, but it's hard to know what that means in the end.

DR. SELF: In the materials, five days seemed to be the cutoff. I guess I would suggest that a relevant group to exclude would be those that died within five days. Might be a little more conservative than other definitions, but that might be --

DR. HUNSICKER: Hunsicker here again.

I want, first of all, to assure the sponsor and my colleagues who were on the experimental team that I have absolutely no suspicion of any hanky-pank. I think that there is no evidence for that, and I think it's right to ask about it, but I don't think it's there.

I think the fact that -- what we have before us is a legitimate randomization before the transplantation and then a random exclusion of patients in the interim between transplantation and when they started medicines, and then a group of people that followed later on.

Now if, in fact, they had stipulated at the beginning that they were going to randomize at the time that people could take oral medicine, I would have had absolutely no question of the legitimacy of excluding those earlier patients. The problem -- I think why we wind up with two different answers is, in fact, chance.

You have a situation where two random events occurred, and they fell out differently. That's all. They just fell out differently. The problem is not that there is a bias that has been injected into here. I don't think that it's likely that there's any bias. The problem is that there were two tests.

You had a test. You decided what your test was, and then, you know, to put sort of the bad face on it, you didn't like what you saw, and so you chose a different one. You know, that just doesn't fly.

DR. ELASHOFF: So which is the right one?

DR. HUNSICKER: I think you got to stick with the one you stipulated and, if you go to the other one, then what you have to do is, just has been discussed, is you have to adjust for the multiple comparisons.

DR. GRIFFITH: Well, maybe I shouldn't be here, because -- or maybe I should, because I seem to be --

DR. GOLDBERGER: Probably you actually should, in fact.

DR. GRIFFITH: I maybe am the lone voice of reason, because I'm not very educated on the

statistical models, and that's obvious by my comments, but in all due respect to my learned colleagues in that regard, I got to deal with patients that are alive or dead, and we've got to come up with a recommendation for this particular sponsor's product relative to this trial.

Now you are making them pay, in my opinion, an incredible tax because of your onerous protocolism, if you wish. These folks screwed it up, if you wish. They wished they could have started it over in terms of protocol, thinking that, you know, if you can't take an oral drug, how can we study it.

It seems to me that by random chance the same number of people who were assigned to the MMF versus azathioprine fell out. That didn't seem fishy to me, that if you can't take a drug, it doesn't matter whether you were assigned to an MMF group or an azathioprine group, if in fact the initial assignment was randomized. Those people couldn't take the drug.

So forget them. Let's address the issue of relevance, and that is let's look at the people that were treated. I'm sorry. I don't see that as being able to look at the thing two ways.

It seems to me that it's the way to look at it. Now because it was designed differently, this

incredibly difficult, expensive and very important trial, I think, is being assigned less than it should be.

To me, I'm only interested in the patients that received the drug, because I think, in fact, that is an intent to treat group, because the patients that fell out of that group, once they received initial therapy, in fact, are included in the treatment analysis.

CHAIRMAN MASUR: Why don't you make a comment. Then we'll come back over here.

DR. EL-SADR: Go back to -- I think your comment is interesting. You're only interested in people that received the drug. However, when they did an on-treatment analysis, there was no difference between the two drugs.

So I think we're sort of beginning to pick and choose what we like. I'm a clinician, too, and I want to find something that works for these patients, but there are, you know -- It seems like we are presented with the one that did show a favorable response in survival.

They did do an on-treatment analysis, looking at analyzing people as they are taking the drug, and that showed no difference in mortality at

all. So I guess, again, I'm --

DR. GRIFFITH: Is that the group that there were 18 deaths in the one group and 33 deaths in the other?

DR. EL-SADR: No, that's the 12 and 14. They did not present the data at all today. I think he mentioned it verbally.

DR. GRIFFITH: Well, in the treated group at a year there were 33 deaths --

DR. EL-SADR: No, not treated. What I mean by on-treatment is patients taking the medication, because the treated group includes people who had to stop medication.

DR. GRIFFITH: Right. But that's an intent to treat trial, which we think is the favorable way to evaluate it.

DR. EL-SADR: But I guess it's again trying to --

DR. GRIFFITH: So they really did an intent to treat trial in the treated group.

DR. EL-SADR: The other comment I had is that are we -- did the people who did not start treatment -- did they -- Was the only reason they did not start treatment, they could not take oral medication? I don't think you told us that.

I think, if that were true, then I would agree with you, but I think it probably was a mix of reasons why people elected not to -- withdrew the consent or elected not to start medication. Right?

DR. MAMELOK: Of the 72 patients we determined that 65 were not able to take oral medication, and that the remaining seven were, and it's not clear precisely why they were withdrawn, but most of them were, in fact, because of their physical condition, unable to take oral medication.

CHAIRMAN MASUR: Well, Michael and Paul, do you want to make a comment?

DR. FLYER: Yes. We don't -- I, in particular, do not disagree with your comments in terms of whether or not it's an important finding or whether it's unlikely to have occurred by chance. I was trying to point out -- Mike was, as well -- that in trials such as this we put a lot of stock in sort of reaching the magical .05 level.

Now that's done in a very specific way statistically. So that what we're suggesting is, in fact, that they might not have reached it, but it's still sort of unlikely to have occurred simply by chance, even if you do an adjustment; but it doesn't really in an unequivocal way sort of reach this

standard that's been accepted in the literature.

So it's obviously important if it's a reduction in 50 percent. It's unlikely to have occurred by chance, but the question is sort of, does it reach that point where we can say unequivocally they've made it, and based on conventional standards maybe they haven't, but it's still -- It's in that range where it's still unlikely to have occurred by chance.

I think I'm agreeing with you, but maybe technically it sort of maybe doesn't meet that magic level, but it's sort of in that ballpark if you try to operate under the tyranny of the p value.

DR. PIANTADOSI: I would just like to add one thing. I'm very sympathetic to Dr. Griffith's comments, but I'm also up to challenges against methodologic rigor.

To be absolutely crystal clear about what's going on here, yes, within this context we have certain deficiencies in our methods of inference in the data that have been presented, but to look at the larger context, the real issue that we're coping with here is the fact that thousands of patients have been treated with azathioprine, and we don't know whether it works or not.

That is a problem of the methodology that's been applied previously and the culture of how these drugs are used and approved and indicated among clinical colleagues and surgeons who utilize them.

So that's in part what we're up against here.

DR. WOODLE: I had one question I wanted to clarify just a little bit, and it's for you, Michael.

When you look at the treated patients between the azathioprine and the MMF treated groups, in terms of risk factors, your analysis of risk factors for either rejection, patient survival or graft survival, are you satisfied with the rigor with which you've applied, that those risk factors are equal between those groups?

DR. ELASHOFF: No. I guess I'd say the number of events is small enough and the number of baseline factors that could be important in that are large enough that I wouldn't be satisfied one way or the other with that kind of analysis. I mean, it just -- It just couldn't --

DR. WOODLE: You analyzed it enough to feel confident that you can't analyze it?

DR. ELASHOFF: Right.

DR. WOODLE: Okay. Thank you.

CHAIRMAN MASUR: One of the issues, if we could just take a short hiatus -- Part of this process is to have an open public hearing, which we were supposed to do between eleven and twelve.

No one came to the committee asking for time, but if there is anyone who as part of an open public hearing would like to make a statement, we'd be willing to consider having them do so now.

Is there anybody who wants to make a statement? Okay. If not, then the open public hearing is closed, and we'll go back to our discussion.

DR. GOLDBERGER: Okay. I just wanted to remind everyone as the discussion progresses, what we're asking you is a somewhat, perhaps more difficult or complex question ultimately than what much of the recent discussion has focused on.

I mean, certainly, it's worth discussing in some detail the issue, did they or did they not show superiority with regard to the 12 month endpoint. I think it's important to do that.

We had considered for a while even asking that as a specific question, but felt that we would see how the discussion flowed and that we would

probably get to that without having to specifically pose it, and I think we were correct about that.

What we're really asking you as a starting point is: Taking into account the results as you've seen them, what you know about some of these issues -- we've talked about early deaths, etcetera -- what you know about the activity of azathioprine -- and this is why we have a mix of people on the committee -- Taking all those things into account and looking at the results, at one level does this meet a sufficient standard to label the drug for the indication versus something else that's also important to get your advice on, I think a lot of which we've already gotten.

If the product were labeled for this indication, would we want, for instance, an unrestricted statement of superiority in the labeling as part of the description versus a variety of caveats about what we know about how well the drug works?

These are not all necessarily the same thing. Evidence may be sufficient to make the product available with certain descriptive phrases in the label stating what we know about it versus having it made available with some clear, unequivocal statements about that it's absolutely superior.

I do want to make a little bit of that distinction here, because I don't want the entire discussion to focus on whether or not it's superior by itself, because we are, unfortunately, enmeshed, as was just pointed out, in this issue of azathioprine, which we are not going to resolve unequivocally during this meeting as to whether it's active or not.

So we are asking for people's best opinion about how we should take into account this comparison versus a drug which we don't have the kind of information we'd like about activity, but which is acknowledged everyone uses, and a clinical trial could not have been done without having it as the control arm.

CHAIRMAN MASUR: Well, Larry, I see wants to respond first to that, but it is an issue as to whether or not any trial can be done based on equivalence in this setting or whether we should demand that superiority be shown, given that the control arm is of unknown efficacy.

DR. HUNSICKER: Well, that wasn't quite the question I wanted to answer.

CHAIRMAN MASUR: We realize, but we give you an opportunity.

DR. HUNSICKER: Well, let me do two things

quickly, and then get to where actually I left off a while ago, which I think is one of the questions you're after.

I personally would require showing superiority to azathioprine, because I am personally, utterly unconvinced that azathioprine adds anything to an adequate immunosuppressed patient on cyclosporine or one of the similar drugs and prednisone. I'll just say that as an opinion, and we'll go on to the next thing, which is:

One of the issues here is the distinction between making the drug available -- this is your phrase -- as opposed to something that I will call attesting to its efficacy.

Now if this were a hearing concerning a drug that was not currently labeled for anything, we would have a rather different circumstance, because the question would be: Is the burden of evidence sufficient to say that we would be doing our patients disservice by not making it available?

As I will comment on a little later on, I'm a little uncomfortable about that, because I -- you know, my sense is that this actually may be an effective agent, but it is, in fact, available off-label.

I will ask you later on, and I don't want to clutter up the current thing now to talk about something I read about recently, which is the change in the law for the FDA which will permit the FDA under certain circumstances to permit marketing an agent off-label.

That is to say, is there a halfway in which we can say, look, there are some data in support of this which you can read; it hasn't met the test of demonstration of efficacy, as it's normally defined, but we do think that these other informations might call to your attention.

I would ask for whatever the agency has to say on that point right now, but I want to get and spend a little bit more time on the issue of the long term mortality, because I think that is really --

When I read the documents, I was utterly unconvinced that there was superiority with respect to rejection, but I was rather taken, as I suspect Dr. Starns was rather taken, by the -- not Starns, I'm sorry; Steve Bartlett. Oh, gosh, you get me all confused -- Bartley Griffith. That's all right. -- by the numeric superiority in survival.

One of the questions which you implicitly ask is, if you have a trial that is set up to show

superiority over here so long as there is equivalence over here, and you don't show superiority over here, but by chance and sort of unintentionally you show superiority over here, what are you supposed to do?

I, for one, would in fact pay a great deal of attention to mortality as a significant factor. I mean, after all, rejection is a matter of treatment and all of that, but what you really care about is whether the patient is surviving.

If you were to find that the patients were surviving better, that would clearly be the basis of an approval, even if it were not really what was intended as the first analysis.

The second question that comes up, and probably the one area in which I sort of disagree with the FDA, is should you then hold these people to what they put into their protocol as a definition of superiority? I would comment that they stated that, in order to be judged superior, you would have to have a ten percent advantage over the opposition.

Now if you start out with an 85 percent survival, it is essentially impossible to achieve a ten percent advantage, and they were probably foolish for having put it quite that way; but again, maybe this is one of the things you learn. You know, you

become smarter when you do these kinds of a trial.

I, for one, would permit them to show me the empiric data at the end of the trial and say, look, the confidence interval doesn't overlap with the same, and I think this is better.

So in that particular case, I disagree with the comments that Mike made that suggested that, since they had stipulated ten percent, we ought to hold them on that, since we would have given them ten percent on the other side.

I'm not sure I would have been happy if they had had significantly inferior outcomes, but it was within the ten percent range, and on that same basis I'm not sure I would write them off just because it wasn't more than ten percent.

So the real issue in my mind, the sticking point, the point that gave me worry as I came to this protocol -- and I see some nods over here; I suspect it's yours -- is that it looks as though patient survive better on this stuff maybe, and how certain are we of that.

This depends, unfortunately, in large measure on your estimate of the impact of azathioprine on survival, for which we have the better of the two sets of evidence.

Now when I thought that it was likely that the analyses from Opeltz and from the Registry had included time, I was going to spot them four points, because that was the best fix that we had, and I was going to say, well, actually, on their primary all patients included everything they had.

They were at least better than four points less than azathioprine. Unfortunately, that has gotten sort of washed away by the fact that it looks now as though those were not time corrected data, and I suspect that there is as much as four points of advantage.

I would also -- I know that the sponsor suggested earlier on that they would take exception to your comments, Mike, about the lack of robustness, and it is true that one patient, one way or the other, would change that; but that also is second guessing. They got what they got.

So if they had really shown superiority in their primary outcome, I would have probably said let's give it to them, and it may well be that Bart is going to vote for it on that basis; but I look at all of this, and there just are too many questions for me to say that they have proved that point, because in fact, in their primary defined analysis, they didn't

make it.

I know you think that I'm full of little red ants, Bart, but you know, you can't -- just don't have too many opportunities or you ruin what you mean when you talk about significance values.

The other thing is that on the primary analysis the relative risk, which -- I would agree with Dr. Piantadosi -- there we go -- that far more attention should be placed on relative risk reductions than on the other.

In their primary analysis, the relative risk reduction is only about 20 percent, reduction 20 percent in death. I calculated that late last night. It is much greater on the patients receiving treatment, but then we have all of these problems of exactly how that -- why that group and how that group was chosen.

So on the balance, I come up with the answer that this one doesn't make it to the point where I would say we should attest to the efficacy of this agent. However, if it were necessary to do something in order to make it available to the doctors who are treating patients, I would do that.

DR. ABERNETHY: I think it kind of keeps coming up, and so I guess I would ask Mike. That's

this issue of what an equivalence trial is as compared to what a trial to demonstrate difference is; because it kind of keeps coming back to, if you're looking at an equivalence trial, then if you show that something is different, that means it's different.

I think we would all around the table accept that, if you're trying to look for differences and you find no differences, that does not mean they're the same.

I think what's happened and is happening is that we're just becoming more and more comfortable with this idea of an equivalence trial, but there still needs to be some education go on.

So, Mike, could you speak to that a little bit?

DR. ELASHOFF: Yes. I think that -- I mean, there is the problem that, if you were to, say, adjust the confidence intervals in the treated analysis, those confidence intervals would include zero.

So on the basis of that, when you have the intent to treat confidence intervals including zero, you have the treated confidence intervals including zero, you're doing equivalence, it seems pretty straightforward that you've demonstrated equivalence.

There is a suggestion perhaps that, with complete longer term follow-up, the advantage might get larger. When that longer term follow-up is available, then a more definitive superiority might result, and that could be indicated.

DR. ABERNETHY: Well, yes, but the point is that that's not the hypothesis that you set out to test. So that one is left with coming back to this comment about, well, next time they'll know better than to spread it as wide as ten percent, because you can't possibly do that.

Well, I can tell you that they're very nervous about narrowing it to five percent, because then they might lose. So in an equivalence trial, really, the thrust that one has to counter is spreading the interval too wide so you can't possibly show nonequivalence.

DR. ELASHOFF: Yes. I mean, I think it comes down to, when you consider doing an equivalence trial, essentially you're hedging your bet, because if it's a little bit worse, you can still get something out of it; whereas, if you did a superiority hypothesis from the beginning, the trial would have been a failure.

So it's that sort of tradeoff that, if

you're a little worse or the same, an equivalence trial leads to demonstration of efficacy.

DR. ABERNETHY: Well, but the whole reason to set it up as an equivalence trial is that there is a therapy that's out there that at least there's a believe is effective, and you're trying to demonstrate that you have something that is equally effective to that therapy.

DR. FLYER: Well, it's not necessarily just equally effective. It could be that it's close enough, given the variability in the trial, to be clinically of interest. So that it doesn't necessarily have to be strictly equivalent.

So it may be a little artificial to make the distinction between testing and confidence intervals, but in the end we have an estimate of how close it is. We have some bounds on it, given the size of the trial, and sort of is that close enough that we're comfortable that the drug is efficacious.

Then the question becomes, well, if we've concluded it's efficacious, how do you describe it relative to the comparative agent, and we're only here because it's questionable.

That's usually what we'll do. If it's a clear bound right around zero and it's nicely

symmetric around zero, there won't be a really major issue; but if it sort of shifts in either direction, we'll end up calling you together, basically, to discuss, well, what has been shown? Are we comfortable about the control arm, the boundaries, things of that sort.

Does that help you at all?

DR. ABERNETHY: I agree. I think the issue is that the lower limit is flirting with zero. You can get it a little above or a little below, depending on how you mix and match things, and it's suggestive; but it's not something that we're all comfortable with.

Imagine that the lower bound was at 2 or 3 percent. Then we wouldn't be going through all these gyrations, I think.

I guess I was sitting here wondering whether -- at what time would some longer term follow-up survival data be available? Say two years. I heard earlier that the effect of AZA kind of tops out at one year, and you know, perhaps there would be some opportunity to look at this in the not too distant future with some really much more compelling data pertinent to the survival endpoint.

CHAIRMAN MASUR: Does the sponsor want to

respond to that?

DR. MAMELOK: Yes. First of all, we do have data with nine months' more follow-up. Could I have slide DX-30, please.

I'm going to show these data both for the enrolled population and for the treated. This is the Kaplan-Meier estimates now. So these are a little different than what you saw before from the point of view in the Kaplan-Meier curve you saw before, it included all patients, but they had all reached the time that we're depicting here.

So these are Kaplan-Meier estimates of survival to 24 months. The patients at risk at 24, 18, 12, 6, and at the start of the trial are shown here with AZA groups in orange and mycophenolate in white, and it's 155 patients and 150 who were at risk at 24 months. That number is smaller than that one, partly because patients die, and they drop out and things like that.

What one sees is, as we pointed out earlier, and this is due to the patients that we've talked a lot about today who never got study drug, the curves crossed at about six months, and the pattern seems to be continuing and holding true at 24 months.

If I could have slide DX-29. This is the

same curve in the treated group, and again the patients at risk in the treated group are here. It's displayed the same way except these lines -- these numbers floated to the top.

Again, the curves separate, and they continue to separate and, in fact, widen, and we have performed confidence interval on the difference of these points.

If I could have slide -- Yes, this is the confidence interval here. This is the Kaplan-Meier estimate of the treatment difference of 8.1 percent, and here the 95 percent confidence interval is the lower limit of 2.5 percent, and the upper limit is 3.8 percent.

DR. PIANTADOSI: Do you have that same slide for the enrolled?

DR. MAMELOK: I'm not sure we have it on a slide, but we should have the data.

DR. PIANTADOSI: Is this Kaplan-Meier two years?

DR. MAMELOK: This is the Kaplan-Meier estimate to two years.

DR. PIANTADOSI: At two years now for the whole curve?

DR. MAMELOK: Pardon me?

DR. PIANTADOSI: At two years --

DR. MAMELOK: Yes. This is the estimate at two years, and these are the confidence interval at the difference estimated at two years.

DR. PIANTADOSI: Have you summarized the data in the form of a hazard or risk ratio rather than just this vertical difference between the curves?

DR. MAMELOK: I'll have to defer to the statisticians on that question. No, we have not.

CHAIRMAN MASUR: In terms of this analysis we at one point had planned to just work through lunch, but since I think we need to do justice to the two questions, after we take the last question maybe we should take a half-hour break and then come back.

Last question, Dr. Pina?

DR. PINA: This may be the same point. As a clinician, which is what I'm here and my role is here today to the FDA, I am very interested in this survival issue of a year to two years.

There's also a secondary endpoint that was one of the secondary objectives of the trial, which was coronary artery disease or allograft vasculopathy, which is what limits a survival of the grafts once you get out beyond that first year.

I am very interested in finding out

clinically what that data is, and there were a subset of patients that actually had IVUS done, because we were an IVUS institution, and I would like to know with intervascular ultrasound what the incidence of transplant vasculopathy is, because if this agent truly can diminish the chances of transplant vasculopathy, then it's an agent that I think merits being used in the population.

CHAIRMAN MASUR: Does the sponsor want to respond to that?

DR. MAMELOK: Yes. May I have slide IVUS 2, please.

The IVUS examination was not performed at all centers, because all centers did not have it available at the time that the trial was initiated. So what we have here -- So this will be an analysis on a subset, which -- I just wanted to be up front about that from the beginning.

There are 289 patients in each group. There are 94 patients in the AZA group and 102 patients in the mycophenolate group who were, in fact, evaluable at IVUS at both baseline and with one year data.

We don't have the data analyzed for IVUS at two years and three years yet, because not all the

patients have gotten there. So this would be, as coronary vascular disease goes, probably somewhat early in the course in terms of observing differences.

I'll show two measurements. If I could have the first, which is IVUS 7, please. This shows the change in maximal intimal thickness, and for this measure there is no difference. The groups are exactly the same.

If I could have IVUS slide 6. This shows, actually, the change in lumen area, which is a measure that's typically done for IVUS, but again I would acknowledge that that was not a specified endpoint, but it is part of the standard IVUS examination and actually gives an estimate of the actual arterial lumen, which is, of course, where the blood flows.

What we can say here is that the lumenal area for mycophenolate was at least preserved. There was an observed mean difference of an increase in the lumenal area of .327, and the lumenal area for azathioprine decreased with a mean decrease of .813 square millimeters in the azathioprine group, indicating that the lumen is getting narrower in the azathioprine group.

I'd like to ask Dr. Kobashigawa, who is really an expert in this field, to comment on these

data.

DR. KOBASHIGAWA: Transplant coronary artery disease is indeed one of the major factors limiting long term survival. It occurs about ten percent per year. So at about five years about 50 percent of patients will have some irregularities on the angiogram.

Now intervascular ultrasound actually is a newer technique. What it is is a catheter that goes into the coronary arteries and has an echo machine at the very tip. We can actually see how thick the coronary artery wall is.

The arteriogram just fills the lumen with dye and does not tell you anything about what is happening in the arterial wall. That's why intervascular ultrasound has become, more or less, the standard to detect transplant coronary artery disease.

We believe that the findings here are interesting, to say the least. It did not show any differences in intimal thickness, but it did show an increase in lumenal area.

Now I think it's a very important piece of evidence, because when you look at some of our natural history studies, the intervascular multi-center study, we saw this decrease in lumenal area.

It's probably what we call negative or constrictive remodeling. It may be due to scarring in the adventitia. We don't think it has anything to do with the intimal, because the intimal area is about the same.

So there may be some scarring in the adventitia which makes the arteries narrower or it may have something to do with the endothelium, the lining of the artery, which is, if we're correct, if it is maintained in its integrity, it will make nitric oxide which will allow -- It's a molecule which will allow the artery to stay open.

We know that endothelial function is very important when one talks about transplant coronary artery disease. If you can maintain endothelial cell function and integrity, perhaps you will then decrease the development of intimal thickness later on.

So I think Dr. Pina's question is quite appropriate in the sense that we may see differences in intimal thickness at the three-year mark.

Since the incidence is rather low, 10 percent per year, at least from an angiographic standpoint, it may not be enough patients, enough time to show difference between the two groups, which we hope to see at the three-year mark.

CHAIRMAN MASUR: Maybe at this point let's take a break until 1:15, and then we'll resume for some final discussion and then focus on the questions.

(Whereupon, the foregoing matter went off the record at 12:49 p.m.)

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A F T E R N O O N S E S S I O N

Time: 1:19 p.m.

CHAIRMAN MASUR: Again, we're going to get ready in one moment. Could we collect all our committee members.

So, Dr. Goldberger, when we start, there's a request that you tell us a little bit about the difference between off-label advertising and approving another indication. What are the different implications?

DR. GOLDBERGER: Okay. Might as well wait until everybody gets here.

CHAIRMAN MASUR: Yes. I see the sponsor is here. Now we just need a few more committee members.

All right, I think we're almost all here. Again, we're going to try to move along to our questions relatively soon, but again there was an issue brought up as to what the implications of approving a new indication are as opposed to potential new regulations allowing the sponsor to advertise based on unapproved indications.

DR. GOLDBERGER: I think I seem to recall, actually, Dr. Hunsicker having sort of asked that question during a couple of the points right before

lunch. So I sort of presume the question may have, in fact, come from him.

CHAIRMAN MASUR: I can't say.

DR. GOLDBERGER: It is entirely appropriate that the Chair deliver it. I have no problem with that.

Basically, as part of the FDA Modernization Act a change was made in the ability of companies to promote products when they are not currently labeled for that. I should point out that the regulations have not yet been written for that. It's in the statute, but the details, basically, do not yet exist.

Conceptually, it would allow a company for a product that is not currently labeled for that indication to submit material from peer reviewed journals to the FDA about 60 days before they intend to distribute the material, to allow FDA a chance to review.

The exact definition of a peer reviewed journal, what FDA's review process is, are -- you know, have not yet been described, but that will presumably occur in the coming months.

So that that process does exist, and is a way to make products available -- you know, make

information available on products that are not labeled for the indication. However, there is another aspect to that, and that is that there needs to be either studies underway or a commitment by the company within X period of time to submit an application to get this product as a labeled indication.

It is not the spirit of this approach to be in a situation where, for instance, an advisory committee has just voted that the product is not safe and effective for the indication and then sort of turn around, I think, and allow promotion for an off-label indication. That is not the spirit of the current changes in the statute.

So I don't think that that's something that would fit in with the modifications, as I currently understand them. So, I mean, it's a useful thing as a bridge while one is in the process of getting together the information.

It may act as an incentive for a company who is interested in doing this to make -- to get information available to physicians, etcetera, but it is not as though it's a substitute for never doing a study or never submitting information to the FDA, and I think it is not really in the spirit of this in a situation where, for instance, an application has been

reviewed and turned down, to then at that point go ahead and do this. That's my current understanding about it, based on the information we received within the last week or two.

CHAIRMAN MASUR: All right. Then one other issue came up. The sponsor wanted to make a brief comment about the one look versus two look process and the statistical implications. So, hopefully, these will be a few brief and well focused comments.

DR. KOCH: The essence of the comment is simply the sponsor had to have statistical significance in the treated population, because if the scenario had been reversed and you had had significance in the enrolled population but no significance in the treated population, the finding would not be meaningful; because the untreated would be leveraging the finding.

A finding is only credible if it produces significance in the treated population. That's why the treated population is logically precedent over the enrolled population, even though the sponsor did not write their protocol that way.

You must win in the treated population to have a meaningful finding. So in that sense, there

are not two opportunities. There must be a win in the treated, and then the enrolled is a higher hurdle.

Unfortunately, the sponsor promised to jump the ten-foot hurdle before promising to jump the five-foot hurdle.

CHAIRMAN MASUR: All right. Anyone on the panel want to comment or respond to that? Steve? Larry? Michael?

DR. ELASHOFF: Well, that may be true for superiority, but for equivalence it might be exactly the opposite, that the overall -- Since it's easier to demonstrate equivalence in the overall analysis, there might have been a definite reason why the intent to treat analysis was kept as primary, even though it was already known ten-eleven percent of people hadn't received the drug.

DR. KOCH: But if equivalence had failed in the treated population, equivalence would not have been believed in the treated population, just as in many cases, if equivalence fails in a per protocol population, the equivalence is not believed.

So even in an equivalence context, the treated population would have a logical priority. Unfortunately, the sponsor didn't say that, but my comment is mainly there were not two opportunities to

win.

The sponsor had to win, whatever they looked at, in the treated population, and then they then have to address the untreated population. What the results are in the untreated population are still, nevertheless, a concern; but this is not an issue that requires the additional penalty of doubling p values.

DR. ABERNETHY: I think, to -- That comment I find interesting, because if you looked in the overall population and you found the result that you wanted to find, you wouldn't look in the treated population. I mean, really now.

DR. KOCH: Of course, you wouldn't look in the treated population, because you would not want to have your overall finding leveraged by people who never received treatment.

In other words, if there was an advantage spuriously in the untreated to those randomized at one treatment over those randomized to another, and that was driving the overall effect in the all-patients analysis, you would essentially have a fallacious result.

You're going to look at the treated population to confirm that the treatment is actually working in those who got it. That's why per protocol

analyses are often required to be confirmatory to intent to treat analyses.

Intent to treat analyses have a priority, because they're perceived as a higher hurdle, but it doesn't mean that they're fully believable. They're only fully believable when they are confirmed by a per protocol analysis.

CHAIRMAN MASUR: Well, I think we have had extensive discussion now about what the most appropriate approach to analyzing this study is. It would appear that we don't have a consensus.

At some point I guess we're going to have to answer or approach the two questions that have been posed to us by the agency, and we're going to have to deal with the issue that there's a difference of opinion about whether azathioprine is a reasonable standard for comparison when we have potentially equivalence rather than superiority as a result.

Are there other issues that -- Larry, you want to frame that better?

DR. HUNSICKER: No, I don't want to frame those things better, but I do want to -- FDA is quite correct, where the question about off-labeling advertising came from.

Your response, unfortunately, doesn't give

me the out I was hoping for. So I need a little clarification here, and I'm going to put this in perhaps bald clinical terms, as I told one of your troops there.

I distinguish between convincing evidence of safety and efficacy, which I believe is the standard which I've been asked to vote on for the FDA, as opposed to the best available evidence. At the current moment, if I were responsible for a cardiac transplantation who had had a severe rejection episode with hemodynamic compromise that was being treated with azathioprine, I'd stop the azathioprine, and I would start the mycophenolate, and I'd do this because I know mycophenolate works in kidneys and because it seems as though maybe it works here.

So there is the issue that I put earlier on of availability. So the question comes up: In a circumstance where you have a drug which is approved on a different indication, where it is available to those of us who want to use it off-label, what is the FDA's intent for us to do where the evidence is not convincing but where the best evidence -- What do you want to say, the preponderance or however you want to define it in those quasi-legal terms -- suggests that the stuff might work?

DR. GOLDBERGER: There's a couple of answers to this, and I hesitate to give a complete answer to part of what you said, since I don't want to be sort of defining regulatory policy here.

The simple answer, of course, is that physicians are free to use the product off-label. The company may not promote it, but you are free to prescribe it. You are free to prescribe it for any type of transplantation that you personally wish to do, and currently there is no effort made to regulate that. However, it may not be promoted by the company.

Currently, I don't believe there's been a change in having information passed out in a situation where there is no intention to do a study or submit a study to get the indication termed as being labeled. So I think that's the short answer to what you said. People are free to do it.

Whether that is the best approach to having patients cared for, one can question, since there may be important information about the use of the product that would be better off being in the product label, leaving aside the issues of the company's ability to promote.

I will mention only in passing one other thing. You did comment about these vague legal terms.

We should remember that drug approval does come specifically from a statute.

The standard in the statute is not convincing evidence. It is substantial evidence. You used the term before preponderance. Preponderance in the law means more than 50 percent, in fact.

The term chosen by Congress in 1962 which, to the best of my knowledge, has not been changed is substantial. Substantial evidence is evidence such that reasonable people might choose to do this even though other reasonable people, including a majority of those, might not. That is the definition from the law, and is what Congress intended, if you read the legislative history of the 1962 amendments.

So that is actually the standard. However, I don't think that that's something we want to get into in great detail, but you may find it interesting to read some of the issues about that; because the standard was never intended to be set in convincing.

CHAIRMAN MASUR: Well, you have to convince us that it will be interesting to read about that.

DR. GOLDBERGER: Very interesting, but we will leave that aside.

CHAIRMAN MASUR: So what other -- Are there other issues that committee members would like to bring up before we get into our questions?

DR. HUNSICKER: One last pursuit of this appearing kind of a thing.

You spoke earlier on about the ways in which labeling could be written, which would -- how shall I say? What I sort of heard you to say, and I'm not saying that it's a quotation, is that this may well be true, but it is not quite the same as it is well established.

What is the range of how you can present this? Bear in mind, you're presenting this, as you well know, to a very small group of doctors who are taking care of cardiac transplant patients who basically are going to know more about this than you do.

The question here then is: If we were to say that we want to make certain that this agent is available to those people who need to use it for this indication, but that we're not 100 percent convinced it really is effective, what is the kind of stuff that can be put into the label to say that?

CHAIRMAN MASUR: Yes, and let me just remind everyone, as I think is clear to everyone

around the table, that, mercifully, we do not have to decide on the labeling language, but that, hopefully, the agency will be influenced by both the vote -- well, this vote is advisory, but hopefully, they will be influenced by the spirit of the discussion also in terms of how they write the labeling, if this is recommended for approval. Mark?

DR. GOLDBERGER: Yes, and I think that that's a very -- you raise a very important point, Henry, that, obviously, beyond the issue of whether or not the product should be labeled, it is helpful to get a sense of what the committee thinks about how it compared, for instance, to azathioprine; because that would influence wording in the label.

For instance -- and we have not at all discussed this with the company. So we're talking now rather hypothetically. You could state, "the product is indicated for this indication" and describe in a section in the label how it was compared to azathioprine, a numerical statement about what was shown for a couple of agreed upon, important endpoints, and a proviso (a) that azathioprine's efficacy has not been proven; or (b) because of multiple comparisons, one cannot make any statement about significance, statements like that that sort of,

I think, modulate the sense a clinician reading it might get about the amount of activity.

Those are the things, and there's a great deal of flexibility in the wording, and that is something that is negotiated between ourselves and the applicant. So there is wording.

In other words, you either are saying that the product is indicated for this or, basically, the application is turned down. I mean, there is no other wording. We cannot word the label to say, well, it might be useful.

That's not, for instance, an option. There is not the gray area there, but there can be statements made within a clinical studies portion that give people a little more perspective on what was shown and how to interpret data from the clinical trial.

That is something that is commonly done. The amount of text that's required like that, obviously, varies from circumstance to circumstance.

CHAIRMAN MASUR: Susan?

MS. COHEN: I come from a consumer protection background. So when I read "there is evidence to suggest MMF may be," it's like being slightly pregnant. It is or it isn't. I mean, to

suggest -- I wouldn't take any medication. I wouldn't want any consumer to take a medication that says it suggested it might be.

I think, if that's the strongest words they can use, then we have to go home and do some more homework. I think that's scary, to me.

CHAIRMAN MASUR: I think that's a good point, although I guess we all recognize, in medicine -- I guess it was suggested before -- we often are making decisions based on data that is not randomized and statistically significant, and the question is whether or not that should be --

MS. COHEN: And that's where they run into trouble.

CHAIRMAN MASUR: -- a basis for approval is something we're going to debate.

MS. COHEN: "Maybe" to me is very weak language, and I find that very frightening.

CHAIRMAN MASUR: Other comments?

DR. STARLING: Yes. I wanted to make a few comments and then ask a question in response to some of the discussion just before the break.

I think it's important to point out for the non-heart transplant experts on the panel that are reviewing this that one of the major perceived

advantages of MMF is its -- at least in laboratory studies, is its efficacy in inhibiting B lymphocyte function in antibody production, as well as some of the data that is presented in the background information on intercellular adhesion, migration of white cells to endothelial cells, etcetera.

The reason why that's important really plays into this whole issue of hemodynamic compromise and rejection that we've struggled with to some degree, because I made a comment earlier today that we really don't know how to diagnose rejection, and rejection is a continuum. It's a spectrum.

We have to put in the context of that that within that continuum is this other issue that's also been discussed, coronary artery disease. The coronary artery disease that heart transplant recipients develop is clearly felt to occur on an immunologic basis.

I think the IVUS information that was presented is very interesting, but I would still argue that the key of this information today and what we're going to see in future studies like this are going to be mortality endpoints and the issue of retransplantation and mortality, when we're talking about a heart transplant recipient.

I think everything that we've talked about, hemodynamic compromise, the IVUS coronary artery disease, all plays into the whole -- There's really some black box here from the standpoint of what the mechanisms of action are of the drug, how much the B cell inhibitory function plays into this, and not even mentioned today was the whole issue of so called humoral or antibody mediated rejection.

The data that's -- and that's because it's such a contentious issue in cardiac transplantation. But a lot of the rejection that we treat clinically -- I know there was a question raised in the room, why would a patient be treated with hemodynamic compromise if the biopsy didn't show much in the way of rejection.

The answer to that is the clinician must always factor into that that this other type of rejection, this antibody mediated rejection that we really don't have a good way of diagnosing may be at play here, which is why I think the message that's coming from all the clinicians on the panel is the emphasis on the mortality data.

So the question that I wanted to ask, if it's been put to any statistical review or if anyone on the panel could comment -- What I'm most impressed

with or one of the things I'm most impressed with is the data that was provided, the slide number 60, showing that those with biopsy proven rejection and severe hemodynamic compromise, of which there were 57 patients.

Twelve of the 57 or 21 percent died, and 12 of the 38 were azathioprine, and none died in the MMF. I think this is a very important piece of clinical information, but I would just ask from a statistical standpoint how much credence you would want us to put into this.

DR. ELASHOFF: Well, one interpretation of these data is that this endpoint is not a good surrogate marker for mortality. A surrogate marker, you would expect to have a strong predictive effect, regardless of treatment, and this didn't meet that.

In the azathioprine it seemed like it was a reasonable predictor. In mycophenolate, it was not. In the untreated population, it was not.

So in those three groups, when it's only sort of a predictor of mortality in azathioprine, it wasn't in mycophenolate. It wasn't in untreated. You have to wonder whether this just means it's not a good surrogate marker for long term survival.

DR. GOLDBERGER: Let me just give you my

observation about this. That was: Assuming that you believe that biopsy proven rejection in the severe hemodynamic compromise is something you wouldn't want to have, my only observation would be there were twice as many people in the azathioprine as in the MMF group, and I would probably, as a starting point, just leave it at that.

CHAIRMAN MASUR: Maybe what we should do now is try to answer the questions, and other issues will come up. I know there are a couple of committee members who have to leave sooner than others, but let me just read the two questions. Then maybe we'll start with Dr. Woodle who, I think, is the first who has to leave.

The two questions, which I think everybody has in their packet are:

Number 1. Is CellCept safe and effective for the prevention of organ rejection in cardiac allograft recipients?

Number 2. Please comment on the design of future cardiac studies, including the choice of control and six-month endpoints.

Steve, do you want to start, and then maybe we'll just go around the table.

DR. WOODLE: Sure, with question 1. The

issue, is CellCept safe: This committee voted when CellCept came up before for its kidney indication that it was safe, and I see really very little reason to believe that the safety of it is any different in cardiac transplantation than it is in kidney transplantation. So would have to vote the same for today.

As far as efficacy, the two areas that are under consideration are equivalence for patient/graft survival. I think we're in agreement there that the issue that's been under considerable debate has been the superiority over biopsy proven rejection.

I think that there is a considerable question or reasonable questions about that. What I do believe is true is that it is at least as effective as azathioprine.

So my answer to question number 1 would be, yes, it is safe and effective. I would like --

CHAIRMAN MASUR: I'm sorry. Are you going to indicate whether or not you think that, based on that, that should be grounds for recommending approval?

DR. WOODLE: The answer is yes.

CHAIRMAN MASUR: Okay. I'm sorry, go ahead.

DR. WOODLE: And as a final comment, I think that we must all remember this is, you know, the first study of its kind that's been done in cardiac transplantation. I think that a lot of the problems that the sponsor has encountered during the study and after the study with analysis is a result of the fact that it's that first attempt, and they are to be commended for making that attempt.

The second issue is that historically immunosuppressive agents have been more effective in other solid organs, particularly kidney and kidney/pancreas, than they have been in liver transplantation. It's important to remember, the high bar is a little bit higher in cardiac transplantation.

It's harder to show immunosuppressive efficacy in hearts than it is in other organs.

CHAIRMAN MASUR: Do you want to make some comments, Steve, about the design of future studies?

DR. WOODLE: No.

CHAIRMAN MASUR: Okay. Actually, why don't we just go around left to right. Larry?

DR. HUNSICKER: I agree that CellCept is safe, and I don't think that that warrants any further comments.

I've been torn, as you can probably tell

from the last bit of discussion, about what to say about effectiveness. I actually agree with Steve that I think the equivalence to azathioprine is solidly established. I'm not sure what that proves, but if that gives me an out to say that I think that we have said that this stuff is equivalent to azathioprine, I'm willing to say that.

I do feel that it should be made available to cardiac transplanters, although I am not at all convinced of its superiority. So I will say yes, and I will actually say, to answer your explicit question, that given the discussion that I've had with Dr. Goldstein, is it, or whatever down there -- Goldberger--

DR. GOLDBERGER: We don't take any offense since you're consistent around the table.

DR. HUNSICKER: The government. And assuming that they will attack with vigor the issue of labeling, I will vote to approve this drug for cardiac transplantation.

With respect to recommendations for further trials, I think these have already come out, and probably have come out and have been absorbed even before this meeting by the sponsor. I believe that, if the agent cannot be given, that the randomization

should be delayed until it is clear that the agent can be given.

I think that it will not prove to be possible to exclude early failures, because you really have to start this drug when the patients become able to start it orally, and I don't think that you should delay admission to a protocol until after the drug has been started. You get into all sorts of problems there.

With respect to the six month endpoint, you probably know as much as any of us do at this point. My own druthers is that the judgment of the individual clinician in a well blinded trial that treatment is necessary is probably the best endpoint.

Had I been in your group, I would have argued strongly for that at the beginning and, in fact, had you done that, you probably would have wound up with a significant value there.

So I think serious consideration ought to be given to making the clinical decision to treat or perhaps some well defined clinical parameters requiring treatment should be the endpoint, and that pathology should be used as supportive rather than definitive.

CHAIRMAN MASUR: Susan?

MS. COHEN: Since I'm not a political person, I really have tremendous problems with the samples they used in the 538. It really troubles me a great deal.

I think they were chosen to be favorable, and so I'm not comfortable with that. The other thing I have to say that makes me uncomfortable -- being consumer member is a lot different.

If we don't expect certain standards, then the message gets out that someone else can come in and not do a good job or not present these things, and that also bothers me; because I'm here representing consumers, and that's what it's about, and thank God someone mentioned at this table consumers.

You don't hear it very often, I'm afraid, but we are the endpoint of everything. I don't set myself up to be a scientist in any way. My husband was at NIH, and so I'm used to science, and I'm just concerned that we can't have some kind of standard that will be acceptable and be met in each time.

I think I'm going to have to vote yes, but with a lot of reservations and concerns that this doesn't send a message out to every other pharmaceutical company, well, you know, in the long run you can get it passed, but I am troubled about how

you put your samples.

CHAIRMAN MASUR: Okay. Ileana, you're not a voting member, but would you want to make a -- We'd be interested in your comments on these questions as well.

DR. PINA: You all know I'm very seldom quiet.

CHAIRMAN MASUR: Most transplant people are never.

DR. PINA: I know. I think the drug is effective. I can tell you from our own clinical status right now that we are using it outside of the study, and we are using it clinically.

I am personally a little surprised at some of the side effect profiles, because we choose it sometimes because of its benefits of the side effect profile. So if I were voting, I would say that, yes, we have to say that it's effective and that it's safe.

I also have my reservations about azathioprine and the way it's been used, because we've never really studied it prospectively, and I was happy to see the discussion, because it kind of gives some credence to my own frustrations with taking care of patients with rejections, and we're often doing things that we're not really knowing how well we're doing

them.

We're sometimes treating patients by our gut sense that something is wrong clinically. I have to agree with Larry that the right decision to treat a patient should warrant concern that something is going on. In other words, if we're going to be aggressive and treat a rejection, that's a rejection that's significant enough to be treated.

Even within our own pathology service, we have disagreements about the reading of slides, and we often go down and look at the slides ourselves, because when we have a question, we'd like to go see it ourselves.

So this is not an exact science, and it is colored by our clinical sense and our clinical decision making, but I think, all in all, that the drug is safe and the drug is effective, and I would vote for it.

I would also vote for changes in the way we perform these trials, and I agree with Ms. Cohen.

CHAIRMAN MASUR: Randy.

DR. STARLING: I'm a nonvoting member, I believe. Correct?

CHAIRMAN MASUR: Yes, that's correct. You're a nonvoting guest.

DR. STARLING: You would like me to make comments?

CHAIRMAN MASUR: I mean, as a guest you're allowed to pass, but we would be interested in your comments.

DR. STARLING: Well, I feel comfortable with the information as presented that the drug should be approved for efficacy, for many of the reasons that I've already elaborated throughout the meeting.

As far as future study design, I think most of the points have already been covered with respect to -- With a drug like this, it's only given orally, randomization at a time point when the patient can take the drug versus at the time the transplant is going to be performed.

The primary endpoint -- I think I learned a lot with this discussion and feel more strongly than before that death and retransplantation should probably be a primary endpoint in immunosuppression studies and cardiac transplant recipients in that they both encompass the issues of death from rejection, degree of immunosuppression, and infectious complications, as well as post transplant lymphoproliferative disorder.

So I think looking at death and

retransplantation at six months and 12 months and on down the line is very important, and I think probably the issue of histologic rate of rejection may more appropriately be a secondary endpoint.

Issues such as coronary artery disease and IVUS play into the results, but probably yield more from a pathophysiologic standpoint and are probably best as secondary endpoints as well.

CHAIRMAN MASUR: Bart.

DR. GRIFFITH: Yes. I believe the drug is safe, and I believe it's effective, and possibly superior to triple drug therapy, cyclosporine, azathioprine and steroids.

CHAIRMAN MASUR: So you would vote for approval?

DR. GRIFFITH: Yes.

CHAIRMAN MASUR: And do you have any additional comments about future cardiac studies?

DR. GRIFFITH: We need to encourage them.

DR. GOLDBERGER: Henry, when you're asking for comments about future studies, one other question, part of that, you might answer is what should the control arm be in those studies. No one has actually said that yet.

I mean, there are several different

possibilities. If people have an opinion, we'd appreciate hearing that.

DR. GRIFFITH: Yes, and it's a very difficult issue, and the control arm sometimes is, obviously, relating to other drugs that the particular sponsor is producing, which -- in other words, a --

DR. GOLDBERGER: Let's assume that it's a situation like this where you're starting with a cyclosporine, for example, based regimen, that you're thinking about substituting for the third product, just to make it simple; but you're absolutely right. It could get much more complex.

DR. GRIFFITH: Yes. I don't think I have anything momentous to say about that. I think that we're stuck with what we have and that cyclosporine, prednisone and immuran appears to be the baseline.

Now if this drug becomes approved, then does this become the new baseline against which other such drugs, such as RAD, will be compared? I don't know that it's easy to come up with that.

So I think for the next three or four years, I'm comfortable comparing all new drugs to this current protocol of azathioprine, steroids and cyclosporine or FK. So --

The other thing is endpoints, which I

think we've struggled with today as much as the azathioprine basis. I think we've learned today that it is very difficult to tag primary endpoint on superiority of rejection at a six month period, and that we recognize that trials longer than one year are difficult to conduct.

So I think that we've seen a greater emphasis placed on survival than what I would have imagined prior to coming and reviewing this particular study. So that maybe more emphasis on survival early on would be of also interest.

CHAIRMAN MASUR: All right. Steve?

DR. PIANTADOSI: Thanks. Yes, I have several comments. First, the bottom line for me would be that I would endorse approval of this product to make it available to the transplant community at large, and I do so with a few qualifications, and I'll say what those are in a minute.

It's pretty clear from this that the trial does not stand on its own, and that's one of the things that we've all been struggling with here. However, I'm not sure that it absolutely has to stand on its own. Clearly, if this was the only evidence that we had available, I think I'd be voting exactly the opposite way.

So I'd modify my normal predisposition not to accept this standard of evidence, as I said earlier, based on several facts. First of all, I don't commend the investigators. I don't think that this is a particularly heroic investigation.

Randomized trials have been around for 50 years. They've been earnestly applied for 30 years, and nobody really deserves especially loud kudos for applying this method in an appropriate application.

This ought to be the kind of thing that's done routinely when these important questions arise in a community, and the methods that we've seen here today really are not a model, in my opinion. They're not something to be strived for. They might be considered a model in transplant surgery, but they are not a model in medicine in general.

Second point: We can't rely too much on the equivalence design and the vagaries of how to make inferences from the fact that the trial was designed as an equivalence study or designed in some other way. The equivalence design is merely a convenience to help us get a sample size and structure for the trial and provides some guidelines for how to interpret the results.

Once the data are in hand, their

interpretation, as far as I'm concerned, is essentially the same as they would be for any other kind of trial design. We've assured ourselves about using an adequate sample size that the failure rates are accurately or fairly precisely measured, and the point estimates are similar to those that would be obtained with azathioprine, and that's sufficient, in my opinion, apart from the nuances of how you design and interpret an equivalence trial, to make those kinds of inferences.

Third point: P values are poor summaries of data. They're poor summaries of evidence, and they should not by themselves drive our inferences. They represent hypothesis tests which are, in some cases, very artificial for the kinds of inferences that we want to make, and the same argument could be made about confidence intervals, which are nothing more than surrogates for hypothesis tests.

Fourth point: Trials such as this one generalize most strongly on a biological basis rather than an empirical one, and in this circumstance we have a considerable amount of reliable biological evidence from renal transplantation where the effect of the drug is arguably the same.

Fifth point: The consequences of a type

1 error in this circumstance, I think, are fairly minimal, and we've already seen pretty good evidence that does stand on its own that the drug is safe.

I say the consequences of a type 1 error are minimal, because the worst case scenario is that we'd be adding a safe but noneffective treatment to a combination that everybody is employing already. I think the consequences of making that mistake are not great.

Finally, the agency can carefully word the indication to reflect accurately the ambiguities that we've all talked about. I would not support any claims whatsoever of superiority for any indication, based on the data, certainly not for biopsy proven rejection, and I would not want to see in the labeling any proof of statistical significance because of the vagaries. Nevertheless, I think that with those two constraints, one could work around them.

For the design of future studies: As I said earlier, randomized trials don't need any endorsement from me. I think that they should be the standard for these important kinds of questions, methods to reduce bias and such as masking and refusal to allow or to make post hoc exclusions of patients based on outcomes, and everything that happens after

randomization is an outcome. I don't care what the clinical motivation is for it.

One can look back and see that the introduction of methodologic rigor in the form of structured experiments in randomized trials has been resisted at nearly every chance by medical practice in the last 50 years, especially true now in surgery where, I think, the real problem, as I hinted earlier, is that the culture and training of surgeons nowadays needs to be changed, despite the rather obvious success stories where this methodology has been used in this field.

So the real problem here that the agency is going to have to cope with is the failure of people to employ good methods, particularly in early development trials, not so much in randomized trials; but good early developmental trials would have helped us quite a lot by showing whether azathioprine was effective or not here.

For the control arm, I can't answer that very well. Placebo or standard of care, and these might be the same in some circumstances, and one could probably generate a pretty credible argument here that placebo is standard of are; but it depends very much on what you believe about efficacy, particularly that

for azathioprine.

The endpoint: I would argue the best endpoint to use for future trials and to insist on by the agency would be overall survival plus retransplantation. All the other endpoints are subject to interpretation, manipulation or the potential errors of surrogacy, and there are many examples of mistakes that have been made when surrogate endpoints were employed in the cardiovascular field, and certainly in cancer and other areas.

So it seems to me that, if you want to develop definitive evidence, one would use survival or retransplantation as the endpoint.

I think also that the agency should endorse and get investigators to accept the importance of the written protocol as a guide in internal calibration, if not only for regulatory purposes, for the types of inferences that are going to come out of the trial at the other end; and there's a real tendency for people to say, well, okay, we wrote it down, but now we'd like to take that back.

Experienced investigators don't do that, and certainly the agency can help them to keep from making the mistakes that follow from that.

Finally, a bit of a hypothetical point: For equivalence, as well as for other kinds of studies, the agency might want to look at some likelihood based methods for analysis and inference rather than trying to rely solely on these deficient p values.

Some of the likelihood based methods are good, because they are free of some of the problems that come from trying to make inferences solely in terms of these artificially constructed hypothesis tests. Thanks.

CHAIRMAN MASUR: All right. Thank you for those comments, Steve. Steve Self, the other Steve.

DR. SELF: I'm certainly convinced that this product is safe, particularly given the risks attendant in this particular patient population. However, I don't think I believe there is substantial evidence that the product is effective for preventing organ rejection in cardiac allograft recipients.

There are -- In the various analyses of rejection with the problems of subset and the different definitions, I really see little evidence that is substantial in this regard, and then there is the uncertain nature of the effect of AZA. So, you know, those, to me, sum up to really not being able to

say that the product is effective for this endpoint.

The survival data is most intriguing. It is somewhat on the edge. I think that some of the comments that have been made earlier about this study not standing on its own are in play here, the experience with renal transplant, and also the risks of what the other Steve has referred to as type 1 errors seem minimal.

I would like to see the survival experience out to at least two years, and that data might ultimately figure into some labeling indication.

So to summarize those comments, I would vote in favor of indicating the drug for this use, and with those caveats in mind.

In terms of design, the issues of how randomization is done, the timing, what the appropriate study population should be, that should be defined -- I think, have been made in the initial comments, and I won't repeat those other than to say, yes, there's some act that needs to be cleaned up there.

I've come to this without any prior experience in this cardiac transplant area. In listening to the discussion this morning regarding the rejection endpoint, it just is a swamp -- opinion

from the outsider.

There is a lot of mechanism that seems to me that needs to be understood before thinking that that kind of an endpoint can credibly be used as a surrogate for what the bottom line, I think, should be in terms of an endpoint for these trials, which is survival and not just six months, one and two year survival in retransplantation.

I think that really should define the primary endpoint for these studies.

With respect to choice of control, I think there are both scientific and practical considerations. It seems that there is a standard, and the available evidence, such as it is, indicates that that might very well be the placebo that we're looking for. So perhaps we could simply label it either publicly or privately as that, and perhaps consider that as the control arm in future trials.

CHAIRMAN MASUR: All right. Darrell?

DR. ABERNETHY: With regard to the first question, I think the data suggests that the safety is okay, and then I think all things put together, I'm persuaded that it could be said to be effective. The data or the evidence, as others have discussed, is certainly based on not only this trial but other data

that's available.

I think the thing that tends to sway me a bit that hasn't been mentioned yet would be the issue of this agent allowing then decreased doses of other immunosuppressive agents with concurrent therapy. I think that -- My comment about effectiveness I want to quality, as one other person did.

I think that there is no data that I have seen that says it's superior to azathioprine. I think that should be clearly laid out in the label, because I sensed throughout the morning that the sponsor was working very hard to bring one to the conclusion that this was better, and I think that the data that they presented us does not support that.

So that's where I am on question number one. On question number two, I guess inadvertently we learned that there is an NDA available or currently being evaluated for intravenous mycophenolate.

I guess that, if one sees how that process goes forward, then one could easily make the case that, in terms of choice of control, if triple therapy is a standard of care -- and I think we've heard the people who work directly in this area all day suggest that it probably is -- then I have to say, I'm left with thinking that probably there's more data on this

agent as a part of the triple therapy than there is for other agents.

That being the case, then one could envision much better control over therapy if they had an IV preparation of all the immunosuppressive agents that were available. So I think in terms of the mechanics of a future control, there may be some opportunities that come up.

I think that's all I have.

CHAIRMAN MASUR: Wafaa?

DR. EL-SADR: I think the evidence we saw today and discussed convinces me that this agent is similar in safety and activity to azathioprine. I did not -- I'm not convinced of superiority. I don't think we saw data today to indicate that it's superior to that other drug.

I use very carefully the word similar in activity, because it's hard to say that it's effective after learning how we started using AZA in general. Nonetheless, I think we have to deal with the reality, and the reality is that it's widely used.

The triple combination is widely used, and probably, although we don't know that -- I'm not convinced that it's better than two drugs. However, still, by necessity this had to be the control arm in

the study. So I think we have to accept that.

As for the design for future studies, I'm going back to a point that I think Susan raised this morning. I know that the data -- the demographics of the population enrolled in the study reflects -- is very similar to other transplant studies and is very similar to actually probably the transplant -- individuals who receive transplants in this country.

I think we can do better. I see a substantial population of patients, African-American, Latinos, who have advanced cardiac disease and who often need the transplants. I think it would be useful for future studies to try to enroll a population that's reflective of those with heart disease, hypertension, etcetera, in the United States.

Another issue is I'm a little bit worried about the whole discussion about when to randomize patients. It seemed to me like people were indicating that we probably should randomize patients later, after the transplant and so when they can take medication.

I'm worried that, by doing that, we'll be becoming more and more selective of our patient population and, therefore, the generalizability of our results will be limited. So I actually like that the

sponsor decided to randomize prior to the transplant. I thought that was the cleanest way to do it, and would hope that studies would still try to randomize as early as possible before clinicians start to select the appropriate patients they feel are likely to benefit from the study.

I think survival should be the primary endpoint, and whether the early survival or later survival, but certainly must be the primary endpoint in this disease.

I'd like to put a plug for involving infectious disease people in these studies to better define the opportunistic events that occurred, and also to maybe have a more uniform way of prophylaxis across the study participants. It would have been helpful to have done that so that we know -- we could better then understand why we saw more herpes events in one arm or another.

It's hard to interpret that, based on the individuals, really, at their sites were using whatever the individual surgeon, I assume -- their standard of care.

I think it would be nice also to have included in studies like this -- maybe you have them already -- some immunologic measurements in these

patients as they went along in the trial, because it seems to me that looking at the immunology of what happens in these individuals is likely to yield some very valuable information and might be again another secondary or subset of patients that can be looked at in more detail than immunologic studies.

I think that's it.

CHAIRMAN MASUR: Well, I'm also impressed with the safety of the drug. It would be nice to have better documentation as to what the rate of infections were or how some of the definitions were arrived; but the drugs do seem to be remarkably free of infectious or immunologic consequences.

It is difficult to evaluate the role of one drug in a combination regimen. I guess that's what we've been struggling with. I don't have anything to add other than that I agree that there is substantial evidence for equivalence, not for superiority, and I'm in favor of approval and look forward to better defined endpoint for rejection and think it's reasonable probably to use an azathioprine combination as a control.

So with that, we need a show of hands of the voting members as to how many would vote in favor of recommending approval. Again, the language for what

it is approved for, how it's stated about equivalence versus superiority, what the precise indication is, will be up to the agency.

The question is: Is CellCept safe and effective for the prevention of organ rejection, should it be recommended for that? We need a show of hands for those in favor.

DR. HUNSICKER: Steve voted for approval.

CHAIRMAN MASUR: Right. Anyone opposed? Anyone I didn't notice? Okay. Yes?

DR. HUNSICKER: A couple of things came up in the course of the going around that I want to answer.

CHAIRMAN MASUR: So it was a unanimous vote in favor of approval.

DR. HUNSICKER: With respect to controls, I would like to adumbrate. I didn't realize that was one of the questions.

First of all, in cardiac transplantation the use of a triple therapy baseline is going to be inevitable for the next period of time, and to try to change that and get people to do a placebo based control is probably futile and not worth the effort to do it.

This then brings up the question of how

can we judge the various kinds of agents that have been used, and maybe I'm going to go a little bit beyond this specific setting to talk about the four classes of agents that are currently used.

To my mind, azathioprine is of not documented benefit in a cyclosporine or generally a calcinorin phosphatase inhibitor based regiment. That's either FK or cyclosporine. I would urge that you strongly push to superiority as a test in that case rather than equivalence, but this is something you all have to do in advance.

Prednisone is probably not worth arguing about, because I don't think anybody is ever going to try to substitute anything for prednisone or, you know, one of the steroids. So I won't comment on that.

Both of the calcinorin phosphatase inhibitors, both -- cyclosporine has been shown to be effective in comparative trials against azathioprine, and FK has been shown to be at least equivalent to cyclosporine. I don't think it's been shown -- in livers, I know, because that was one of the specific things we did.

So I think that you can assume that those are active comparators, were one ever to use them as

a comparator.

With respect to induction antibody, I would recommend to you that only one antibody has been shown -- one antibody used as induction has been shown in properly done trials to improve outcomes, and that is diclizamap, and the other ones.

Therefore, if you were to get into a situation where people insisted upon using induction antibody with something else, I would suggest again that you look for superiority.

So my comments are that the areas where we don't really know there's a benefit is from azathioprine and induction antibodies, other than declizamap, and those you should shoot for superiority as a criterion.

With respect to the issue of whether rejection should be an endpoint rather than death, I would just comment that I've actually written a paper about basically the increasing impossibility of doing clinical trials with patient death or organ failure as the outcome.

As you can see, the success rates now for any reasonable period of time are on the order of 85-90 percent, and the sizes of those trials becomes impossible. As a member of the transplant community,

I have to assert that it is essential that we be able to do clinical trials for some endpoint so that we can evaluate the utility of new drugs, getting them out there so that we can actually get the experience we need.

The transplant community is unique in having extraordinary nationwide databases which permit us to get long term information on these things and do the follow-up studies that I think are essential for us to know the other parts of things, but I think that it is essential that we develop other criteria besides simply patient survival at a year or any reasonable short period of time, because studies will not be feasible otherwise.

What kinds of endpoints should we consider? Well, early acute rejection is a reasonable one. I have also in print argued that it cannot be used as a surrogate for survival. I don't think that that's a fair way to do it, but rejection itself is an adverse event.

Anybody who has treated a patient with rejection knows the patients don't like it. It's expensive. It gets them in the hospital and worries the bejesus out of them, and to be able to avoid rejection is a perfectly legitimate, clinically

relevant outcome all on its own. It doesn't need to be tied to anything else. It is not a surrogate outcome.

With respect to the ability to define rejection, I believe that it is difficult, but it is not impossible, and you all know that you don't have to be 100 percent right about pathophysiology in order to identify an endpoint. You just have to have an endpoint that is reasonably strongly related to what you think you're studying.

So that it is possible to define rejection in a way that could perfectly well serve as an endpoint for a study, recognizing that it is not a surrogate for long term survival. It is simply a value on its own to be able to avoid rejection.

Sorry for always having something more to say, but I did want to add those comments to what had been said about trial design.

DR. SELF: I guess I need to respond a bit. You know, it's perfectly reasonable to put forward some rejection type endpoint as a primary endpoint, not as a surrogate for survival. However, to the extent that that does not capture the larger clinical impact of an intervention, it is inadequate by itself.

We've heard discussion here before about this notion of looking at an effect on rejection, but also needing to look at survival to make sure that there isn't some compensation --

DR. HUNSICKER: I agree with actually the endpoint as it was defined, which is a reduction in acute rejection episodes with equivalency with survival. I think that's a very reasonable thing. You certainly have to show that you aren't killing people in order to get a less important interim event, yes.

DR. SELF: But the argument would lead you to trials with design that have longer term follow-up with survival as an outcome.

DR. PIANTADOSI: Not to put too fine a point on it, that was my concern exactly, that it's quite possible to conjure circumstances where you would have improvements in short term rejection that actually would be harmful in terms of long term survival. That has to be avoided. We've already learned that lesson the hard way.

DR. HUNSICKER: Yes, there's no question about that at all.

DR. SELF: I guess one final point is to argue that trials would be -- with survival would be

too large to be feasible. Yet in the next breath there is a description of this wonderful network that was generating large databases.

I'm not sure how to reconcile those two. It sounds to me like there is --

DR. HUNSICKER: Well, I could say read my article, but when you're doing 2,000 transplants a year --

CHAIRMAN MASUR: We'll do that, along with Dr. Goldberger's material on substantial evidence.

DR. PINA: Let me address database. The database is made up of input of all the cardiac transplant centers' activity. It has generated prospective trials, but that's not been the -- The primary purpose initially of the database, was to get the data together, which I think has been immensely helpful.

So maybe one of the things that the group should look at is more prospective trials coming from the group together.

CHAIRMAN MASUR: Well, I think on behalf of the committee, I'd like to express our thanks to the FDA evaluation team for a very insightful analysis, and to the sponsor for providing data and graciously answering all of our questions.

So this meeting is adjourned. Again, we appreciate all our guest consultants' advise.

(Whereupon, the foregoing matter went off the record at 2:23 p.m.)

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